Effective Health Care Program

Comparative Effectiveness Review
Number 117

Pulmonary Arterial Hypertension: Screening, Management, and Treatment

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Prepared by:
Duke Evidence-based Practice Center
Durham, NC

Investigators:
Douglas C. McCrory, M.D., M.H.S.
Remy R. Coeytaux, M.D., Ph.D.
Kristine M. Schmit, M.D., M.P.H.
Bryan Kraft, M.D.
Andrzej S. Kosinski, Ph.D.
Alicea M. Mingo, M.D.
Lisa M. Vann, M.D.
Daniel L. Gilstrap, M.D.
C. William Hargett, M.D.
Njira L. Lugogo, M.D.
Brooke L. Heidenfelder, Ph.D.
Rachael Posey, M.S.L.S.
R. Julian Irvine, M.C.M.
Liz Wing, M.A.
Karen Pendergast, M.P.H.
Rowena J. Dolor, M.D., M.H.S.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input.

We welcome comments on this systematic review. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

Carolyn M. Clancy, M.D.
Director
Agency for Healthcare Research and Quality

Jean Slutsky, P.A., M.S.P.H.
Director, Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Stephanie Chang M.D., M.P.H.
Director, EPC Program
Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Elisabeth U. Kato, M.D., M.R.P.
Task Order Officer
Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

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Key Informants

In designing the study questions, the EPC consulted several Key Informants who represent the end-users of research. The EPC sought the Key Informant input on the priority areas for research and synthesis. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual Key Informants.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any conflicts of interest.

The list of Key Informants who participated in developing this report follows:

Neil C. Jensen, M.H.A., M.B.A.
Director, Cardiology Networks
United Healthcare
Edina, MN

Vallerie V. McLaughlin, M.D.
Director, Pulmonary Hypertension Program
University of Michigan
Ann Arbor, MI

Debjani Mukherjee, M.P.H.
Associate Director, Evidence-Based Medicine, Science & Quality
ACCF/AHA Guideline Staff
Washington, DC

Lewis J. Rubin, M.D.
Critical Care Medicine
University of California, San Diego
La Jolla, CA

Sharad Vora, M.D.
Carolina Pulmonary Medicine
Cary, NC

Technical Expert Panel

In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

The list of Technical Experts who participated in developing this report follows:

James Klinger, M.D.
Associate Professor of Medicine
Brown University
Providence, RI

Jonathan R. Lindner, M.D.
Cardiology
Oregon Health & Science University
Portland, OR

Vallerie V. McLaughlin, M.D.
Director, Pulmonary Hypertension Program
University of Michigan
Ann Arbor, MI

Stuart Rich, M.D.
Clinical Professor of Medicine
University of Chicago Medicine
Chicago, IL

Lewis J. Rubin, M.D.
Critical Care Medicine
University of California, San Diego
La Jolla, CA

Nelson B. Schiller, M.D.
Professor in Residence, Department of Medicine (Cardiology)
University of California, San Francisco
San Francisco, CA

Rubin Tuder, M.D.
Director, Program in Translational Lung Research
University of Colorado, Denver
Denver, CO

C. Michael White, Pharm.D.
Professor and Head, Department of Pharmacy Practice
University of Connecticut
Storrs, CT

Peer Reviewers

Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report does not necessarily represent the views of individual reviewers.

Peer Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential non-financial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential non-financial conflicts of interest identified.

The list of Peer Reviewers follows:

Nicholas Hill, M.D.
Pulmonary and Critical Care Division
New England Medical Center
Tufts University School of Medicine
Boston, MA

Alan L. Hinderliter, M.D.
Cardiologist and Internist
Associate Professor of Medicine
University of North Carolina School of Medicine
Chapel Hill, NC

Bryan H. Ristow, M.D.
Internal Medicine, Cardiovascular Disease
California Pacific Medical Center
San Francisco, CA

Pulmonary Arterial Hypertension: Screening, Management, and Treatment

Structured Abstract

Objectives. Pulmonary arterial hypertension (PAH) is a rare and progressive disease associated with increased pulmonary vascular resistance that, if unrelieved, progresses to right ventricular pressure overload, dysfunction, right heart failure, and premature death. PAH is more prevalent in some populations, thereby warranting screening of asymptomatic individuals. This review seeks to evaluate the comparative validity, reliability, and feasibility of echocardiography and biomarker testing for the screening, diagnosis, and management of PAH; to clarify whether the use of echocardiography or biomarkers affects decisionmaking and clinical outcomes; and to determine which medications are effective for treating PAH and whether combination therapy is more effective than monotherapy.

Data sources. We searched PubMed®, Embase®, and the Cochrane Database of Systematic Reviews for relevant English-language comparative studies.

Review methods. Two investigators screened each abstract and full-text article for inclusion, abstracted data, rated quality and applicability, and graded the strength of evidence. Random-effects models were used to compute summary estimates of effect where several similar studies provided estimates.

Results. Sixty studies involving 7,096 patients evaluated biomarker tests, echocardiography, or both to screen for PAH. Symptom status of study populations consisted of asymptomatic (3 studies; 481 patients), symptomatic (41 studies; 4,394 patients), mixed (8 studies; 1,186 patients), and symptoms not described (8 studies; 1,035 patients). N-terminal pro-B-type natriuretic peptide (NT-proBNP) showed moderate correlation with right heart catheterization (RHC) hemodynamic measures and a great deal of variability between studies in its diagnostic accuracy and discrimination; however, one good-quality prospective cohort study suggested that biomarker testing with NT-proBNP might be useful in ruling out PAH in patients with symptoms suggestive of PAH who have elevated systolic pulmonary artery pressure (sPAP) by echocardiography. No data are available regarding combined echocardiography and biomarker screening in asymptomatic patients at high risk for PAH. Echocardiography estimates of pulmonary artery pressures (sPAP, tricuspid gradient [TG], and tricuspid regurgitant jet velocity [TRV]) and PVR (TRV/velocity-time integral of right ventricular outflow tract [VTI_{RVOT}]) demonstrated good accuracy in screening for PAH, but accuracy varied with the prevalence of PAH in study populations.

Ninety-nine studies involving 8,655 patients evaluated biomarker tests, echocardiography, or both to evaluate severity or prognosis and followed progression of disease or response to therapy. B-type natriuretic peptide (BNP) showed moderate correlation with most RHC measures (mean pulmonary artery pressure [mPAP], PVR, cardiac index, right atrial pressure [RAP]) and clinical measures of disease severity (6-minute walk distance [6MWD]) and showed weak correlation with pulmonary capillary wedge pressure (PCWP), indicating that BNP levels alone could not serve as an accurate surrogate marker for disease severity. Echocardiography-derived

sPAP showed strong correlation with RHC-sPAP with a precise summary effect estimate, although there was a great deal of heterogeneity of results among individual studies. BNP level (summary hazard ratio [HR] 2.42; 95% confidence interval [CI], 1.72 to 3.41) and presence of pericardial effusion were strong predictors of mortality (summary HR 2.43; 95% CI, 1.57 to 3.77) RA size and uric acid were also predictive of mortality, but fractional area change (FAC) showed no significant ability to predict mortality, and data on TAPSE were insufficient.

Thirty-seven studies involving 4,192 patients assessed the effectiveness of drug treatments for PAH in adults. Few deaths were observed in these limited duration studies, leading to wide CIs and lack of statistical power to detect a mortality difference associated with treatment. All drug classes demonstrated increases in 6WMD when compared with placebo, but comparisons between agents were inconclusive. Combination therapy also showed improved 6WMD compared with monotherapy, but the diversity of treatment regimens and the small number of combination therapy trials again make comparisons between specific regimens inconclusive. The odds ratio (OR) of hospitalization was lower in patients taking endothelin receptor antagonists or phosphodiesterase-5 inhibitors compared with placebo (OR 0.34 and 0.48, respectively), while the reduction in patients taking prostanoids compared with placebo was similar but not statistically significant. Each drug class showed a favorable impact on at least two of the three hemodynamic outcomes: cardiac index, mPAP, and PVR.

The applicability of these findings is limited by the relative lack of diagnostic studies among asymptomatic patients and, in prognostic and diagnostic studies, inadequate description and apparent diversity of disease etiology and severity.

Conclusions. Further confirmation is needed to determine if the combination of echocardiography and the biomarker NT-proBNP is sufficiently accurate to rule out PAH when testing symptomatic patients. In asymptomatic populations, more research is needed to permit conclusions regarding their effectiveness for screening. BNP, RA size, presence of pericardial effusion, and uric acid had prognostic value in patients with PAH, but other echocardiographic parameters and biomarkers either were not predictive or had insufficient data. Although no studies were powered to detect a mortality reduction, monotherapy was associated with improved 6MWD and reduced hospitalization rates. Comparisons of different drug combinations were inconclusive regarding a mortality reduction but suggested an improvement in 6MWD when a second drug was added to existing monotherapy.

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Background

Epidemiology and Etiology of Pulmonary Arterial Hypertension

Pulmonary arterial hypertension (PAH), a subcategory of pulmonary hypertension (PH), is a rare and progressive disease whose prevalence is estimated to be between 15 and 50 cases per 1 million adults.[1] While the pathophysiology is not well understood, both genetic and environmental factors have been found to contribute to changes in the pulmonary vasculature, causing increased pulmonary vascular resistance. This increased resistance, if unrelieved, progresses to right ventricular pressure overload, dysfunction, and ultimately right heart failure and premature death.[2] The causes of PAH are numerous and are listed in Table A, taken from the Fourth World Symposium on PAH (2008).[3] Before the availability of disease-specific therapy in the mid-1980s, the median life expectancy at the time of diagnosis was 2.8 years.[1,4]

Table A. Updated clinical classification of pulmonary hypertension (Dana Point, 2008)[a]

1.	**Pulmonary arterial hypertension (PAH)**
1.1	Idiopathic PAH
1.2	Heritable
1.2.1	BMPR2
1.2.2	ALK1, endoglin (with or without hereditary hemorrhagic telangiectasia)
1.2.3	Unknown
1.3	Drug and toxin-induced
1.4	Associated with:
1.4.1	Connective tissue disease
1.4.2	HIV infection
1.4.3	Portal hypertension
1.4.4	Congenital heart diseases
1.4.5	Schistosomiasis
1.4.6	Chronic hemolytic anemia
1.5	Persistent pulmonary hypertension of the newborn
1'.	**Pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH)**
2.	**Pulmonary hypertension owing to left heart disease**
2.1	Systolic dysfunction
2.2	Diastolic dysfunction
2.3	Valvular disease
3.	**Pulmonary hypertension owing to lung diseases and/or hypoxemia**
3.1	Chronic obstructive pulmonary disease
3.2	Interstitial lung disease
3.3	Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4	Sleep-disordered breathing
3.5	Alveolar hypoventilation disorders
3.6	Chronic exposure to high altitude
3.7	Developmental abnormalities
4.	**Chronic thromboembolic pulmonary hypertension (CTEPH)**

Table A. Updated clinical classification of pulmonary hypertension (Dana Point, 2008)[a] (continued)

5.	**Pulmonary hypertension with unclear multifactorial mechanisms**
5.1	Hematologic disorders: myeloproliferative disorders, splenectomy
5.2	Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis: lymphangioleiomyomatosis, neurofibromatosis, vasculitis
5.3	Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4	Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

ALK1 = activin receptor-like kinase type 1; BMPR2 = bone morphogenetic protein receptor type 2; HIV = human immunodeficiency virus

[a]Fourth World Symposium on PAH in Dana Point, CA (2008).

Table reprinted from the Journal of the American College of Cardiology, Vol 54, No. 1, Suppl S, Simonneau G, Robbins IM, Beghetti M, et al., Updated Clinical Classification of Pulmonary Hypertension, Pages No. S43-54, Copyright 2009, with permission from Elsevier.[3]

Screening and Diagnosis

There are two separate populations for which screening for PAH needs to be considered. First, there are patients with symptoms that raise the suspicion of PAH. The symptoms of PAH can be insidious and nonspecific and may include shortness of breath, fatigue, weakness, chest pain, syncope, leg swelling, and abdominal distention. Symptoms that are present at rest suggest advanced disease.[1] Since these symptoms are nonspecific, screening may be necessary to help the physician decide whether the patient should undergo a diagnostic workup for PAH, or whether other conditions should be considered. The other population is patients with medical conditions that put them at risk for PAH. In these patients screening tests may be used to identify patients with asymptomatic elevation of pulmonary artery pressures, who might be more closely monitored for the development of symptoms or progressive disease or offered a diagnostic workup for PAH and possibly treatment for early disease.

Once screening indicates the possibility of PAH, diagnostic tests are necessary to confirm the presence of elevated right-sided heart pressures and to exclude valvular, primary myocardial, chronic lung disease, thromboembolic disease, and miscellaneous other causes of pulmonary hypertension (PH). The reference standard for diagnosing PAH is right heart catheterization (RHC), which is invasive but generally safe. In a retrospective and prospective study by Hoeper et al.,[5] the rate of serious complications in patients undergoing RHCs for evaluation of pulmonary hypertension was 1.1 percent and included bleeding, vasovagal reactions, systemic hypotension, arterial injury, hypertensive crisis, pneumothorax, and cardiac arrhythmias. The procedure-related mortality was 0.055 percent.[5]

RHC not only confirms the diagnosis of PAH but also provides prognostic hemodynamic information (mean right atrial pressure [mRAP], pulmonary vascular resistance)[6] to direct treatment decisions. A small subset of patients with PAH, when challenged with a short-acting pulmonary vasodilator, will experience a drop in mean pulmonary artery pressure of at least 10 mmHg (20%) to below 40 mmHg while maintaining cardiac output; this predicts a favorable long-term response to calcium channel blockers.[1]

Since PAH is a progressive disease, regular reassessment is needed to monitor response to treatment and adjust prognosis. In addition to the assessment of clinical symptoms, RHC has traditionally been the means by which patients' clinical course is monitored; however, transthoracic echocardiography has emerged as a possible alternative monitoring mechanism because of its availability, safety, and relatively low cost. The number of echocardiographic modalities has increased substantially, providing unique insights into the structure and function

of the right heart in patients with pulmonary hypertension.[7] However, this test has not been definitively validated as a substitute for RHC in patients with PAH. Finally, the role of biomarkers has not been fully established in the management and prognosis of PAH. Defining whether biomarkers alone or biomarkers plus echocardiography might be superior to echocardiography alone for informing treatment decisions is a necessary first step in establishing a noninvasive, multifaceted approach to the management of PAH.

Role of Echocardiography

The role of echocardiography in the diagnosis and management of patients with PAH has evolved over time, and has been proposed for screening, assessing prognosis and evaluating response to treatment. Screening high-risk individuals for PAH generally begins with a transthoracic echocardiogram.[8] Echocardiography can estimate the right ventricular systolic pressure and identify other signs of PH including increased right-sided chamber size and wall thickness. Most often, the peak velocity of the tricuspid regurgitant (TR) jet is measured by Doppler and—along with an estimate of right atrial pressure (RAP) based on inspiratory collapse and size of the inferior vena cava—TR jet is used to estimate the systolic pulmonary artery pressure (sPAP). However, a significant proportion of patients have no measureable TR jet. Estimates are often inaccurate compared with RHC; up to 60 percent of echocardiography estimates were more than 10 mmHg off from RHC measurement in one large multicenter registry of PAH patients.[9]

Furthermore, sPAP is dependent on right ventricle (RV) systolic function and stroke volume. In later stages of PH, RV function deteriorates, which can lessen the degree of sPAP elevation and lead to an underestimate of pulmonary vascular resistance (PVR). More recent echocardiographic-based methods have focused on evaluating RV systolic function. Therefore, although transthoracic echocardiography is the standard screening test for PAH, it is less than completely accurate and there is uncertainty as to which echocardiographic measurements are most useful.

Several studies have investigated the use of echocardiography in establishing prognosis in PAH. In a study of patients with systemic sclerosis (n=155), 3-year survival rates were lower in 47 patients with right ventricular systolic pressure (RVSP) $\geq$36 mmHg as calculated by Doppler echocardiography compared with patients with RVSP <36 mmHg (67% vs. 86%, $p < 0.01$).[10] Another study of patients with PAH (n=80) using echocardiography to calculate right ventricular free wall strain found that patients with strain worse than -12.5 percent were associated with increased 6-month disease progression and increased mortality at 1 year (unadjusted hazard ratio 6.2).[11] Uncertainty remains regarding which echocardiographic measure(s) have prognostic value, although tricuspid annular plane systolic excursion (TAPSE) and pericardial effusion have been proposed.[12]

Traditionally, RHC assessment of hemodynamics is recommended to demonstrate treatment response;[12] echocardiography has seldom been studied in this role.

Role of Biomarkers

Because of the limitations of echocardiography, the potential role of biomarkers in screening for and managing of PAH has been the subject of increasing interest over the last decade. Brain natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) are two biological substances found in the blood that have been studied as a screening test in patients at risk for PAH and which have been shown to correlate well with the presence of disease.[13,14] Other biomarkers

currently under investigation include atrial natriuretic peptide, endothelin-1, uric acid, troponin T, nitric oxide, asymmetric dimethylarginine, cyclic guanosine monophosphate, D-dimer, and serotonin. Several of these biomarkers have been shown to correlate with prognosis and mortality, either alone or in conjunction with other traditional measurements such as the 6-minute walk distance (6MWD) test, functional class assessment, and pulmonary hemodynamics.[15] Select biomarkers may even be superior to traditional testing. Patients with idiopathic and familial PAH were shown to exhibit dysregulation over a broad range of inflammatory cytokines, such as tumor necrosis factor-alpha and interleukin-6, when compared with healthy controls, findings which correlated better with prognosis than 6MWD and pulmonary hemodynamics.[16] It remains uncertain to what extent the correlations and case-control comparisons offer valid prognostic information for individual patients and can be used to make better management decisions.

Treatment Strategies

Medications

There has been rapid development and approval of vasodilator medications for PAH over the past three decades. Currently, there are four main classes of medications used to treat PAH:[17]

- Calcium channel blockers:
  - Amlodipine
  - Diltiazem
  - Nifedipine
- Prostacyclin analogues:
  - Epoprostenol
  - Iloprost
  - Treprostinil
- Endothelin receptor antagonists:
  - Bosentan
  - Ambrisentan
- Phosphodiesterase type 5 inhibitors:
  - Sildenafil
  - Tadalafil

These PAH medications have been shown to improve dyspnea, 6MWD, pulmonary hemodynamics, and functional class. Calcium channel blockers are associated with long-term (>1 year) improvements in hemodynamics and functional status in most of those patients who show acute vasoreactivity testing response; however, acute vasoreactivity is seen in a minority of patients tested.[18] The limited usefulness of calcium antagonists—as well as the poor prognosis and diminished quality of life associated with PAH—reinforces the need for new drug therapies and improved delivery of current medications. Limited data suggest that epoprostenol and bosentan may provide a survival benefit; however, this end point has not been studied consistently between the medications.[19] The three medications most recently approved by the U.S. Food and Drug Administration for PAH are: (1) inhaled treprostinil, a new delivery system for this prostacyclin analogue, (2) tadalafil, a new phosphodiesterase type 5 inhibitor, and (3) ambrisentan, an endothelin receptor antagonist. With the exception of tadalafil, these new medications were discussed in the Expert Consensus Document on Pulmonary Hypertension released in 2009 by the American College of Cardiology Foundation and the American Heart

Association.[19] Since then, however, numerous studies have been published regarding the safety and efficacy of these new medications. Also, more data have been published on the older medications for PAH. These new data may clarify any effect on mortality and gauge the comparative effectiveness of these drugs.

Additionally, combination drug therapy (using multiple drugs with different mechanisms of action) is an important area of research and may be the most promising way to improve clinical outcomes although at higher cost.[2] Combination therapy was addressed in the 2009 ACCF/AHA publication, and several studies have since been published on this topic. In order to optimize PAH care, newer information regarding the latest drugs and combination therapies should be systematically reviewed.[17]

Scope and Key Questions

This comparative effectiveness review was funded by the Agency for Healthcare Research and Quality (AHRQ). It was designed to evaluate the comparative validity, reliability, and feasibility of echocardiography and biomarker testing for the diagnosis and management of PAH in addition to clarifying whether the use of echocardiography and biomarkers affects decisionmaking and clinical outcomes. We also wanted to address which medications are effective for treating PAH and how the newer medications compare with older ones and with each other. Further, there was a need for clarity about whether combination therapy is more effective than monotherapy and what effect monotherapy or combination therapy has on intermediate-term and long-term outcomes.

The Key Questions (KQs) considered in this comparative effectiveness review were:

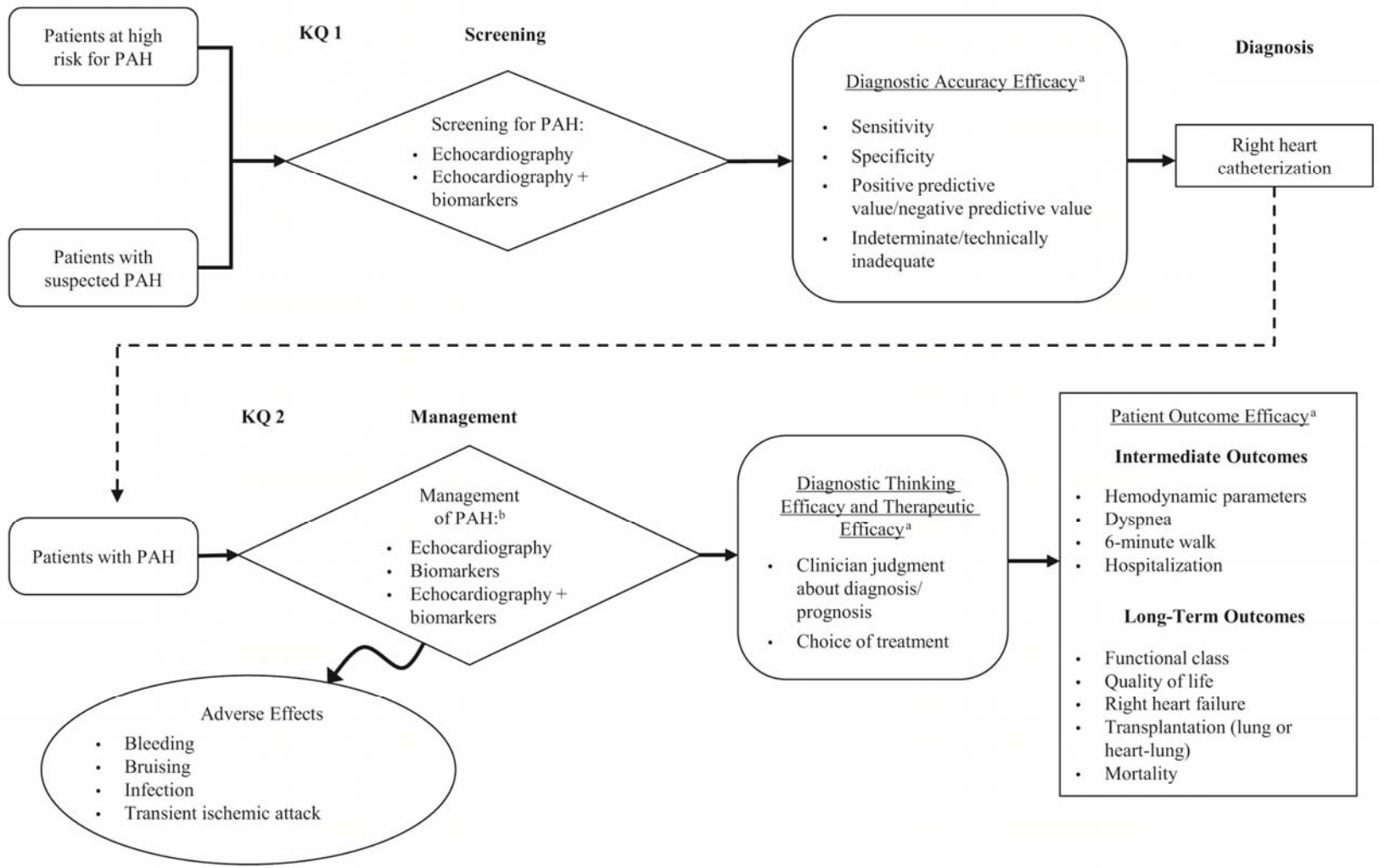
KQ 1: For patients with suspected pulmonary arterial hypertension (PAH) and asymptomatic patients at high risk for PAH, what are the comparative effectiveness and safety of echocardiography versus echocardiography plus biomarkers as screening modalities before right heart catheterization to establish the diagnosis of PAH (i.e., what is their comparative diagnostic accuracy efficacy)?

KQ 2: For patients with PAH, what are the comparative effectiveness and safety of (a) echocardiography versus biomarkers and (b) echocardiography versus echocardiography plus biomarkers in managing PAH and on intermediate-term (≤90 days) and long-term (>90 days) patient outcomes?

KQ 3: For patients with PAH, what are the comparative effectiveness and safety of monotherapy or combination therapy for PAH using calcium channel blockers, prostanoids, endothelin receptor antagonists, or phosphodiesterase inhibitors on intermediate-term and long-term patient outcomes?

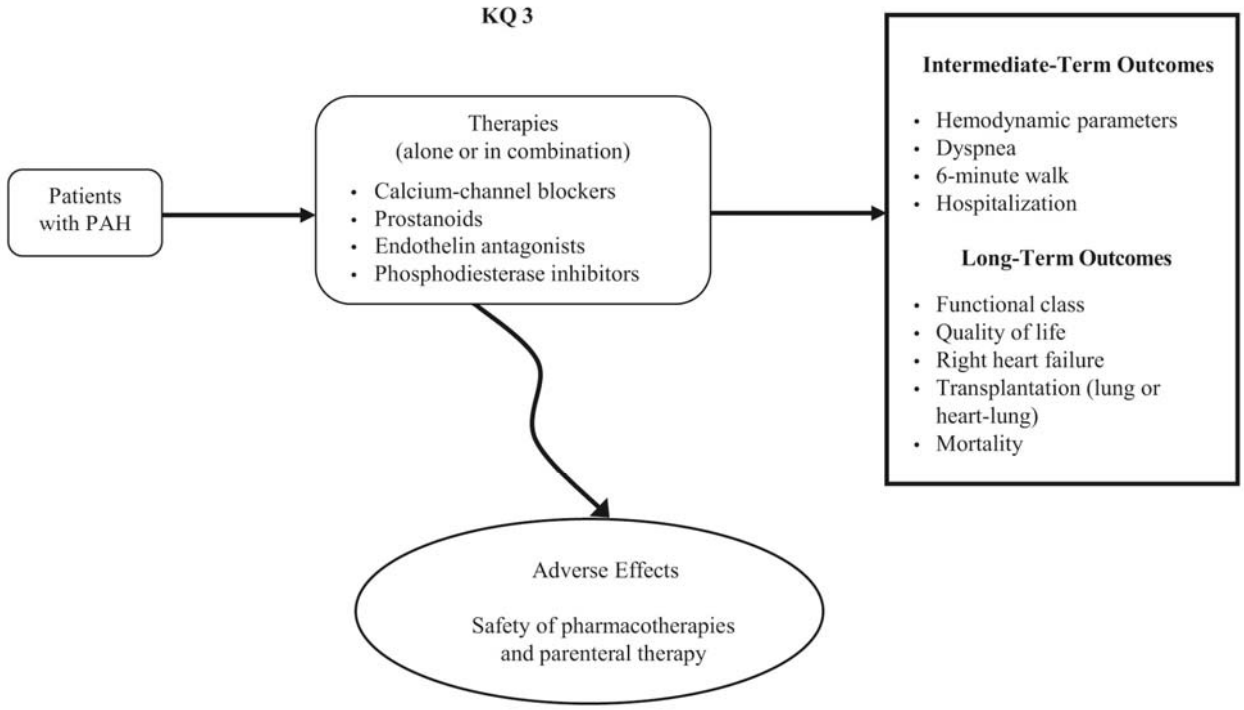
Figures A and B show the analytic framework for this comparative effectiveness review.

Figure A. Analytic framework for KQs 1 and 2



KQ = Key Question; PAH = pulmonary arterial hypertension
[a]Fryback DG, Thornbury JR. The efficacy of diagnostic imaging. Med Decis Making 1991;11(2):88-94.
[b]In conjunction with routine clinical assessment (functional class, dyspnea, 6-minute walk).

Figure B. Analytic framework for KQ 3



KQ = Key Question; PAH = pulmonary arterial hypertension

Methods

The methods for this comparative effectiveness review follow those suggested in the AHRQ "Methods Guide for Effectiveness and Comparative Effectiveness Reviews" (available at www.effectivehealthcare.ahrq.gov/methodsguide.cfm; hereafter referred to as the Methods Guide).[20]

Input From Stakeholders

During the topic refinement stage, we solicited input from Key Informants representing clinicians (in pulmonology, cardiology, and pathology), patients, scientific experts, and Federal agency officials, to help define the KQs. The KQs were then posted for public comment for 30 days, and the comments received were considered in the development of the research protocol. We next convened a Technical Expert Panel (TEP), comprising clinical, content, and methodological experts, to provide input in defining populations, interventions, comparisons, or outcomes as well as in identifying particular studies or databases to search. The Key Informants and members of the TEP were required to disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Any potential conflicts of interest were balanced or mitigated. Neither Key Informants nor members of the TEP did analysis of any kind or contribute to the writing of the report.

Literature Search Strategy

To identify the relevant published literature, we searched PubMed®, Embase®, and the Cochrane Database of Systematic Reviews. We limited the search to English-language studies conducted from 1995 to the present for KQs 1 and 2, and 1990 to the present for KQ 3; prior to 1990, newer drug treatments were not available and prior to 1995 older echocardiographic and biomarker testing technology was less applicable. We supplemented the electronic searches with a manual search of citations from a set of key primary and review articles. All citations were imported into an electronic database (EndNote® X4; Thomson Reuters, Philadelphia, PA).

We also searched the gray literature of study registries and conference abstracts for relevant articles from completed studies. Gray literature databases included ClinicalTrials.gov; metaRegister of Controlled Trials; ClinicalStudyResults.org; World Health Organization International Clinical Trials Registry Platform Search Portal; and ProQuest COS Conference Papers Index. Scientific information packets were requested from the manufacturers of medications and devices and reviewed for relevant articles from completed studies not previously identified in the literature searches.

Inclusion and Exclusion Criteria

Criteria used to screen articles for inclusion/exclusion at both the title-and-abstract and full-text screening stages are detailed in the full report. For KQ 1, the search focused on studies that reported the accuracy of echocardiography, biomarkers, or the combination of these tests for diagnosis of PAH in patients suspected of having PAH or in asymptomatic patients at high risk for PAH. For KQ 2, the search focused on English-language studies describing data on how echocardiographic or biomarker testing among patients with PAH was related to diagnostic thinking efficacy and therapeutic efficacy (clinician judgment about diagnosis or prognosis or choice of treatment) and patient outcome efficacy (prognosis related to intermediate and long term outcomes, including hemodynamic parameters, dyspnea, 6MWD, functional status, and mortality). For KQ 3, the search focused on the effect of pharmacotherapy with prostanoids (epoprostenol, treprostinil, iloprost), endothelin receptor antagonists (bosentan, ambrisentan) or phosphodiesterase inhibitors (sildenafil, tadalafil) on intermediate-term and long-term outcomes as well as adverse effects in patients with PAH. For KQ 3, we chose not to use composite endpoints such as time to clinical worsening (TTCW) due to weighting issues and lack of comparability among studies.

Study Selection

Using the prespecified inclusion and exclusion criteria, two reviewers independently examined titles and abstracts for potential relevance to the KQs. Articles included by any reviewer underwent full-text screening. At the full-text screening stage, two independent reviewers read each article to determine if it met eligibility criteria. Disagreements were resolved by discussion or by a third-party arbitrator, if needed. Relevant systematic review articles, meta-analyses, and methods articles were flagged for hand-searching and cross-referencing against the library of citations identified through electronic database searching. All screening decisions were made and tracked in a Distiller SR database (Evidence Partners, Inc., Manotick, ON, Canada).

Data Extraction

The investigative team created data abstraction forms and evidence table templates. Based on clinical and methodological expertise, two investigators were assigned to the research questions to abstract data from the eligible articles. One investigator abstracted the data, and the second overread the article and the accompanying abstraction to check for accuracy and completeness. Disagreements were resolved by consensus or by obtaining a third reviewer's opinion if consensus was not reached between the first two investigators.

Quality Assessment of Individual Studies

We evaluated the quality of individual studies using the approach described in the Methods Guide.[20] To assess methodological quality, we employed the Methods Guide strategy to: (a) apply predefined criteria for quality and critical appraisal and (b) arrive at a summary judgment of the study's quality. To indicate the summary judgment of the quality of the individual studies, we used the summary ratings of good, fair, or poor. For studies of diagnostic tests (KQ 1 and KQ 2), we used QUADAS-2,[21] a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. QUADAS-2 describes risk of bias in four key domains: patient selection, index test(s), reference standard, and flow and timing; each domain is rated as having high, low, or unclear risk of bias. For studies of pharmacotherapies, we used the Cochrane Risk of Bias tool, which evaluates random sequence generation, allocation concealment, blinding of participant and personnel, blinding of outcome assessment, completeness of outcome data, completeness of outcome reporting, and other indications that the studies are unbiased.

Two raters independently evaluated each study and resolved differences by consensus; if they could not reach consensus, they rated the item as unclear, and the rationale for each differing assessment was described. They described results for individual domains. If the distribution of ratings permitted, they examined methodological domains for association with the effects obtained in meta-analysis.

To indicate the summary judgment of the quality of the individual studies, we used the summary ratings of good, fair, or poor based on the studies' adherence to well accepted standard methodologies and the adequacy of their reporting.

Data Synthesis

Quantitative synthesis (i.e., meta-analysis) was done when we found multiple studies of similar design, population, intervention, comparator, and outcome that reported sufficient data for analysis. When a meta-analysis was appropriate, we used random-effects models to quantitatively synthesize the available evidence. We use meta-analyses both to quantify and to attempt to explain between-study variation as well as to calculate summary estimates. When a meta-analysis was not appropriate we described the reasons, presented data in tabular form, and summarized studies either individually or qualitatively.

For sensitivity and specificity data, we used a binomial model to calculate summary estimates of sensitivity and specificity and associated confidence intervals and summary receiver operating characteristic (ROC) curve using SAS statistical software. Sensitivity analyses were conducted using summary ROC meta-analysis using the diagnostic odds ratio with dr-ROC software (Diagnostic Research Design and Reporting; Glenside, PA). For meta-analysis of correlation coefficients and hazard ratios for observational studies, we used a random effects

model implemented in SAS (SAS Institute Inc.; Cary, NC). For treatment effects meta-analysis, we used a random effects model meta-analysis implemented in Comprehensive Meta-Analysis Software (Version 2.2.064, Biostat; Englewood, NJ). We tested for heterogeneity using graphical displays and test statistics (Q and I^2 statistics), while recognizing that the ability of statistical methods to detect heterogeneity may be limited, particularly when the number of studies is small. We present summary estimates and confidence intervals in our data synthesis.

Strength of the Body of Evidence

The strength of evidence for each KQ was assessed using the approach described in the Methods Guide.[22] In brief, the approach requires assessment of four domains: risk of bias, consistency, directness, and precision. Additional domains were used when appropriate: dose-response association, impact of plausible residual confounders, strength of association (magnitude of effect), and publication bias. These domains were considered qualitatively, and a summary rating of high, moderate, or low strength of evidence was assigned after discussion by two reviewers. A grade of insufficient was assigned when no evidence was available or when evidence on the outcome was too weak, sparse, or inconsistent to permit any conclusion to be drawn.

Diagnostic evaluation studies (KQs 1 and 2) are generally indirect, as the link between the test intervention and outcome is mediated by prognosis, management, and the effectiveness of treatments. As a rule of thumb, we considered correlation coefficients greater than 0.7 as strong association, 0.40 to 0.69 as moderate, and less than 0.40 as weak. In our summary strength of evidence assessments for KQs 1 and 2, lack of directness was weighed less heavily and risk of bias most heavily. Thus, we allowed high strength of evidence levels despite the lack of directness among these studies.

Applicability

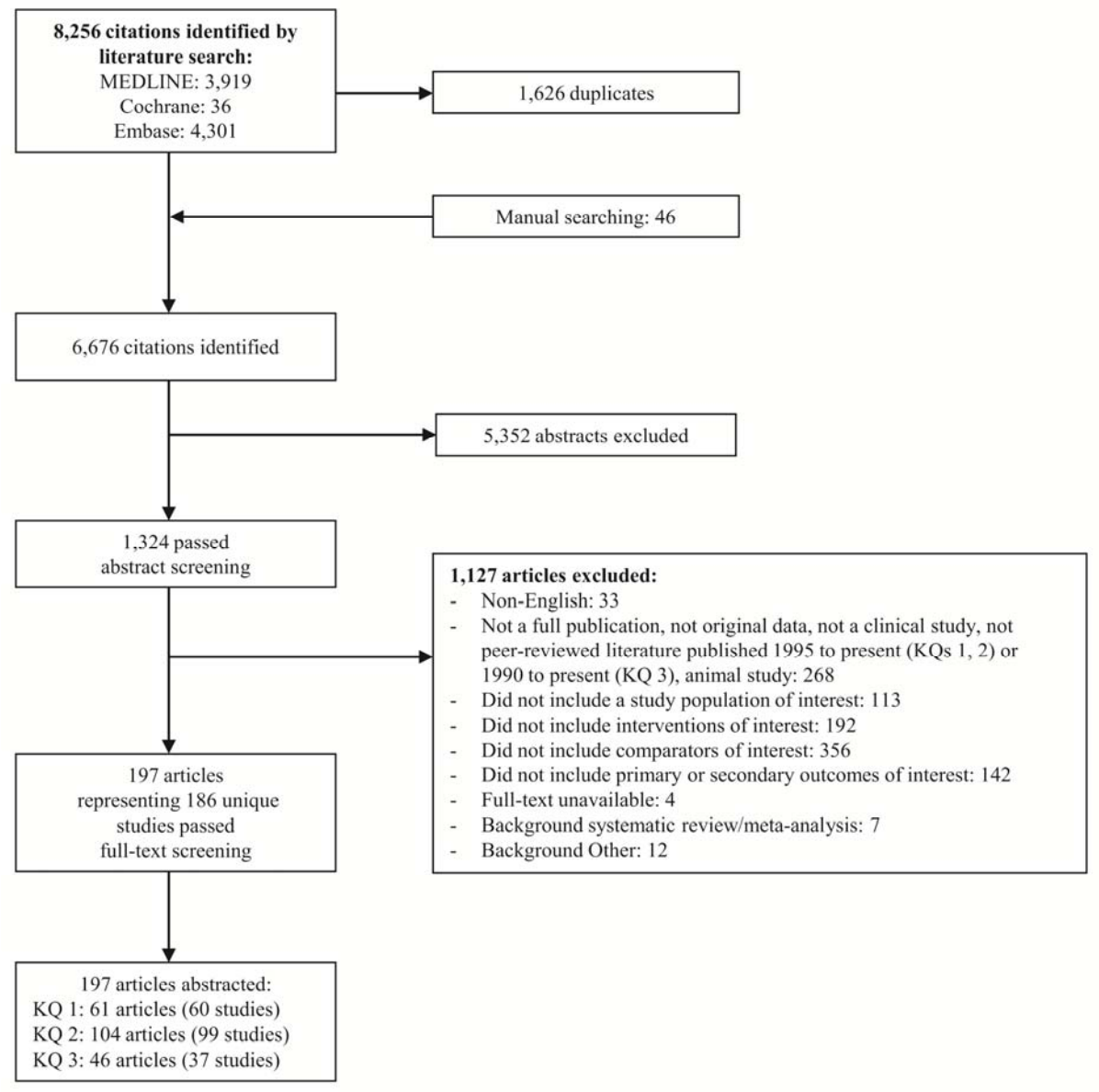
We assessed applicability across our KQs using the PICOTS format as described in the Methods Guide.[20,23] We used these data to evaluate the applicability to clinical practice, paying special attention to study eligibility criteria, demographic features of the enrolled population (such as age, ethnicity, and sex) in comparison with the target population, the version or characteristics of the intervention used in comparison with therapies currently in use (such as specific components of treatments considered to be supportive therapy), and the clinical relevance and timing of the outcome measures. We summarized issues of applicability qualitatively. Because applicability issues may differ for different users, we reported across a range of potential applicability issues.

In assessing the applicability of diagnostic evaluation studies, we were particularly concerned about the prevalence of PAH versus PH in the study populations compared, the spectrum of underlying type of PAH, and the assessment of adverse events associated with testing. In assessing PAH drug trials, we were particularly concerned with whether the researchers had assessed the severity of illness; the use of run-in periods; attrition before randomization; the use of surrogate or combined outcome measures; short study duration; the reporting of adverse events, in particular including those related to administration or monitoring of treatment; whether the sample size was sufficient to assess minimally important differences from a patient perspective; and the use of intention-to-treat-analysis.

Results

Figure C depicts the flow of articles through the literature search and screening process. Searches of PubMed®, the Cochrane Database of Systematic Reviews, and Embase® yielded 8,256 citations, 1,626 of which were duplicate citations. Manual searching identified 46 additional citations, for a total of 6,676 citations. After applying inclusion/exclusion criteria at the title-and-abstract level, 1,324 full-text articles were retrieved and screened. Of these, 1,127 were excluded at the full-text screening stage, leaving 197 articles (representing 186 studies) for data abstraction. (Article counts by KQ do not add to 197 because some studies were included for multiple KQs.)

Figure C. Literature flow diagram



KQ = Key Question
Note: Some studies were included for multiple KQs.

KQ 1: Screening for Pulmonary Arterial Hypertension

Key Points from the Results chapter are:

- For patients suspected of having PAH with elevated sPAP by echo, additional testing with the biomarker NT-proBNP may identify more patients who do not have PAH, compared with echo sPAP alone (based on one good-quality prospective cohort study) (low strength of evidence).
- For patients suspected of PAH, echocardiographic estimation of RVSP (or TG) by TRV, sPAP by TRV and RAP, and PVR by ($TRV/VTI_{RVOT)}$ shows reasonably good accuracy, compared with RHC (moderate strength of evidence).
- Both for asymptomatic patients at high risk for PAH and for symptomatic patients suspected of PAH, natriuretic peptide testing (with either BNP or NT-proBNP) shows highly variable sensitivity and specificity estimates (not simultaneously high) for pulmonary hypertension (PH) or PAH diagnosis (low strength of evidence) and moderate correlation with hemodynamic measures by RHC (moderate strength of evidence).
- There were no studies of the safety of biomarker and echocardiography testing, nor were there any studies of combined echocardiographic and biomarker screening of asymptomatic patients at high risk for PAH (insufficient strength of evidence).

We identified one good-quality study involving 372 patients that compared echocardiography with echocardiography plus biomarkers in patients with suspected PAH, most of whom were symptomatic. There were no other studies that directly compared combinations of echocardiographic and biomarker testing. In order to draw inferences about the comparative effectiveness of other tests, we reviewed the diagnostic accuracy of independent echocardiographic or biomarker testing compared with RHC. By evaluating the relative diagnostic performance of these tests versus a reference standard of RHC, one can impute the comparative effectiveness via indirect comparisons. We identified 60 unique studies involving a total of 7,096 patients that describe the effectiveness of echocardiography or biomarkers in patients with suspected PAH, or in asymptomatic patients at high risk for PAH, as screening modalities before RHC to establish the diagnosis of PAH. Symptom status of study populations consisted of asymptomatic (3 studies; 481 patients), symptomatic (41 studies; 4,394 patients), mixed (8 studies; 1,186 patients), and symptoms not described (8 studies; 1,035 patients). Table B summarizes the findings of our review and the strength of evidence ratings for the available outcomes of sensitivity, specificity, correlation coefficients, and adverse effects of biomarker and echocardiographic tests. Details about the specific components of these ratings (risk of bias, consistency, directness, and precision) are available in the full report. Among biomarker studies, natriuretic peptide (BNP, NT-proBNP) was the only biomarker reported in more than one study; therefore it is the only biomarker for which we generated a strength of evidence table. Limited data on cyclic GMP, asymmetric dimethylarginine (ADMA) and endothelin-1 were reported in one study each. Likewise, the echocardiographic estimates of sPAP and PVR (TRV/VTI_{RVOT}) were the only echocardiographic parameters reported in a sufficient number of studies to support strength of evidence rating. Limited data on FAC, RA size, RIMP, RV size, tricuspid lateral annular systolic velocity (S'), and TAPSE are described in the full report.

Table B. Summary of strength of evidence and effect estimates for echocardiography versus echocardiography plus biomarkers as screening modalities for PAH (KQ 1)[a]

Test	Sensitivity	Specificity	Correlation With RHC
Echo sPAP with NT-proBNP vs. Echo sPAP in symptomatic patients	SOE = Insufficient (1 study, 121 patients) NT-proBNP >80 pg/mL has a low false negative rate compared with RHC reference standard; the serial testing study design did not allow for NT-proBNP testing to improve sensitivity beyond that of echo sPAP alone.	SOE = Low (1 study, 121 patients) NT-proBNP ≤80 pg/mL ruled out PAH in 9–16% of patients with elevated echo sPAP ≥36 mmHg.	SOE = Insufficient (No studies)
Echo sPAP with NT-proBNP vs. Echo sPAP in asymptomatic patients	SOE = Insufficient (No studies)	SOE = Insufficient (No studies)	SOE = Insufficient (No studies)
NT-proBNP compared with RHC	SOE = Low (3 studies, 198 patients) NT-proBNP has variable sensitivity (range, 56% to 100%) for diagnosing PAH; uncertain performance for ruling out PAH.	SOE = Low (3 studies, 198 patients) NT-proBNP has variable specificity (range, 24% to 95%); uncertain performance for ruling in PAH.	SOE = Moderate (3 studies, 176 patients) Correlation of NT-proBNP and RHC is only moderate (range, 0.43 to 0.72).
TRV/TG/sPAP compared with RHC	SOE = Moderate (19 studies, 2,459 patients) Echocardiographic estimate of sPAP showed variable sensitivity ranging from 58% to 100%, with lower prevalence studies finding higher sensitivity.	SOE = Moderate (19 studies, 2,459 patients) Echocardiographic estimate of sPAP showed variable specificity ranging from 50% to 98%, with lower prevalence studies finding higher specificity.	SOE = Moderate (23 studies, 4,217 patients) Echocardiographic estimates of sPAP showed moderate to strong correlation (range, 0.38 to 0.96) with RHC and were on average unbiased, but were limited by imprecision and by a significant minority of patients in whom TRV was not measurable.
TRV/VTI_{RVOT} compared with RHC	SOE = Moderate (6 studies, 196 patients) Echocardiographic estimate of PVR showed reasonably high sensitivity (range, 89% to 100%) for ruling in PAH.	SOE = Moderate (6 studies, 196 patients) Echocardiographic estimate of PVR showed variable specificity (range, 50% to 97%), with better specificity in lower prevalence studies (range, 94% to 97%).	SOE = High (6 studies, 196 patients) Showed strong correlation between echocardiographic estimates of PVR and PVR by RHC (range, 0.74 to 0.84).

NT-proBNP = N-terminal pro-B-type natriuretic peptide; PVR = pulmonary vascular resistance; RHC = right heart catheterization; SOE = strength of evidence; sPAP = systolic pulmonary artery pressure; TRV = tricuspid regurgitant jet velocity; VTI_{RVOT} = velocity-time integral of right ventricular outflow tract

[a]Shaded background indicates insufficient strength of evidence.

One good-quality study evaluated the diagnostic value of serum NT-proBNP in a noninvasive diagnostic decision algorithm that also used data from electrocardiography and echocardiography. Among 69 patients without RV strain on ECG, serum NT-proBNP level >80 pg/mL had 100 percent sensitivity and 24 percent specificity. Taken in combination with the decision algorithm, and in patients with echocardiographic estimates of sPAP ≥36 mmHg, the presence of either RV strain on ECG or serum NT-proBNP >80 pg/mL had a sensitivity of 100 percent and specificity of 19 percent for diagnosis of PAH based on the RHC reference standard. By using this decision algorithm to exclude precapillary PH, the investigators concluded that 9 percent of referred patients with elevated sPAP by echocardiography (≥36 mmHg) could avoid undergoing invasive RHC. After excluding patients with RV strain, serum NT-proBNP testing would have avoided RHC in 16 percent of patients.

Fourteen studies (4 good quality, 7 fair, and 3 poor) evaluated biomarkers in patients both with and without PAH. Most studies were of natriuretic peptide (serum NT-proBNP or BNP); we found one study each for urinary cGMP, ADMA, and plasma endothelin-1 (ET-1). Sensitivity and specificity estimates associated with natriuretic peptide among four studies that permitted their calculation were highly variable, presumably reflecting differences in study populations because differences in test thresholds did not result in the expected direction of change in sensitivity and specificity. The remaining 10 studies reported statistically significant correlation coefficients between natriuretic peptide levels and hemodynamic measures CO, mPAP, PVR, and sPAP.

Nineteen studies (6 good, 10 fair, 3 poor) reported the diagnostic accuracy of echocardiographic estimates of pulmonary pressures based on TRV measurement, with or without estimate of RAP, compared with a reference standard diagnosis based on RHC. Summary estimates for sensitivity (0.90; 95% CI, 0.80 to 0.96) and specificity (0.87; 95% CI, 0.80 to 0.92) showed moderate heterogeneity (I^2=61.9%). Studies with lower prevalence of PH (less than 15% of study subjects) showed greater homogeneity than studies with higher prevalence of PH (sensitivity 0.84 [95% CI, 0.72 to 0.91]; specificity 0.84 [95% CI, 0.72 to 0.91]). The 10 low-prevalence studies (sensitivity 0.91 [95% CI, 0.85 to 0.94]; specificity 0.91 [95% CI, 0.85 to 0.94]) included 4 studies of liver transplant patients (which had complete verification of test-negative subjects) and 6 studies that had high degrees of verification bias.

Seven studies (3 good, 3 fair, 1 poor) evaluated the echocardiographic estimation of PVR using TRV/VTI_{RVOT} against RHC diagnosis of elevated PVR. Three of these studies included patients with known PH. Two studies used a threshold for PVR much higher than that used for diagnosis (8 Wood units vs. 2 Wood units), with the goal of distinguishing more severe PAH; these studies also used a higher test threshold of 0.2 and 0.38 compared with 0.14 to 0.175. Sensitivity ranged from 57 to 94 percent, while specificity ranged from 57 to 100 percent. Because of clinical heterogeneity no meta-analysis was performed.

Six studies correlated TRV/VTI_{RVOT} with PVR by RHC. Correlation coefficients indicated strong correlation ranging from 0.73 to 0.84, with bias ranging from 0 to 6.1, and standard deviations ranging from 1.9 to 4.3 Wood units.

We found no studies describing the safety (or harms) of echocardiography or biomarker testing.

KQ 2: Management of PAH

Key points from the Results chapter are:

- No data are available regarding the comparative effectiveness of echocardiography versus biomarkers or echocardiography versus echocardiography plus biomarkers with respect to the management of PAH or patient outcomes (insufficient strength of evidence).
- sPAP estimated by echocardiography shows good correlation with sPAP from RHC (low strength of evidence).
- BNP level shows moderate correlation with these RHC measures: mPAP (moderate strength of evidence), PVR (low strength of evidence), RAP (moderate strength of evidence), cardiac index (low strength of evidence), and clinical outcomes such as the 6MWD test (moderate strength of evidence).
- BNP level shows poor correlation with RHC pulmonary capillary wedge pressure (PCWP) (low strength of evidence).
- BNP level alone is not an accurate surrogate marker for disease severity (high strength of evidence).
- Increase in level of log-transformed BNP is a strong predictor of mortality (moderate strength of evidence).
- Presence of pericardial effusion is a strong predictor of mortality, although there was wide variability in results for this measure (moderate strength of evidence).
- Right atrial (RA) size correlates with increased risk of mortality (moderate strength of evidence).
- FAC is a poor predictor of mortality, but results are variable across studies (moderate strength of evidence).
- Serum uric acid level appears to predict mortality (low strength of evidence).
- TAPSE has inconsistent association with mortality (insufficient strength of evidence).
- We found no studies addressing diagnostic thinking efficacy, therapeutic efficacy, or harms (insufficient strength of evidence).

We identified 99 unique observational studies, involving a total of 8,655 patients, that evaluated the use of biomarkers or echocardiographic parameters in the management of PAH or as predictors of patient outcomes. Of these studies, 68 were rated good quality, 29 fair quality, and 2 poor quality. We did not find any studies that assessed the comparative effectiveness of echocardiography versus biomarkers, or echocardiography versus echocardiography plus biomarkers, as outlined in our original KQ. Instead, we focus on available studies that evaluated the ability of echocardiography or biomarkers to assess the severity of PAH, to predict events such as lung transplantation or death, or to assess a patient's response to therapy. By evaluating the independent association of biomarkers or echocardiography, one can impute the comparative effectiveness via indirect comparison. The most common biomarker evaluated was BNP (59 studies), followed by uric acid (9), endothelin-1 (6), troponin T (4), nitric oxide (2), cGMP (2) and ANP (1). We found no studies assessing D-dimer or asymmetric dimethylarginine to evaluate their ability to assess severity of disease, response to therapy, or outcome.

Thirty-nine studies evaluated several echocardiographic parameters. These included sPAP (17 studies), RIMP/MPI/Tei (14), RA size (11), pericardial effusion (11), RV size (9), FAC (8), mPAP (8), TAPSE (6), TR jet (4), TRV/VTI_{RVOT} (3), RVEF (2), echocardiography-derived cardiac index (2), and RVSP (2).

For the comparators, we focused on RHC hemodynamics, 6MWD, and functional class (FC) as the reference standards for assessing severity of disease. Thirty-four studies used RHC as a reference test, 15 studies used 6MWD as a reference test, and 10 studies used FC as a reference test.

Thirty-nine studies looked at correlation between biomarkers and/or echocardiographic parameters and the comparators. Twenty-three studies evaluated hazard ratios (HR) for death, two studies evaluated HR for a composite outcome of death or lung transplant, and one study evaluated HR for lung transplant alone. Twenty-three studies evaluated changes in mean values in response to therapy, and four studies evaluated changes in median values in response to therapy. Eight studies assessed mean or median change from baseline in response to therapy.

In studies evaluating correlation of the above measures with RHC measures or a commonly used measure of disease severity (6MWD) studies were too underpowered to give reliable results. However, by combining studies looking at the same parameters and performing a meta-analysis we were able to increase the power for seven different comparisons: (1) BNP versus RHC-mPAP, (2) BNP versus RHC-PVR, (3) BNP versus RHC-CI, (4) BNP versus RHC-RAP, (5) BNP versus RHC-PCWP, (6) BNP versus 6MWD, and (7) echocardiography-derived sPAP versus RHC-sPAP. BNP showed moderate correlation with most RHC measures (mPAP, PVR, cardiac index, RAP) and clinical measures of disease severity (6MWD) and showed weak correlation with PCWP. Most effect estimates were precise (mPAP, PVR, cardiac index, RAP, 6MWD), but estimates for PCWP were imprecise, making it difficult to interpret the clinical importance of the findings for this measure. For the other measures, correlation with BNP was only moderate, indicating that BNP levels alone could not serve as an accurate surrogate marker for disease severity. Echocardiography-derived sPAP showed strong correlation with RHC-sPAP, although there was a great deal of heterogeneity among these studies and only moderate strength of evidence to support the use of this measure.

In studies evaluating the ability of biomarkers or echocardiographic measures to predict mortality, we were able to perform a meta-analysis on six measures: BNP, pericardial effusion, RA size, FAC, uric acid and TAPSE. BNP level and pericardial effusion were strong predictors of mortality. RA size was also predictive of mortality. Data on uric acid suggested an association with mortality, while fractional area change (FAC) showed uncertain association with mortality.

The strength of evidence ratings for the most commonly reported biomarkers and echocardiographic parameters are summarized in Table C (management of PAH) and Table D (prediction of patient outcomes).

Table C. Summary of strength of evidence and effect estimates for the use of echocardiography or biomarkers in the management of PAH (KQ 2)

Comparison	Number of Studies (Patients)	Summary Correlation Coefficient Estimate (95% CI)	SOE and Findings
BNP compared with RHC-mPAP	14 (606)	0.39 (0.31 to 0.47)	SOE = Moderate Serum BNP level shows moderate correlation with mPAP.
BNP compared with RHC-PVR	13 (684)	0.46 (0.31 to 0.59)	SOE = Low Serum BNP level shows moderate correlation with PVR.
BNP compared with RHC-RAP	12 (645)	0.47 (0.40 to 0.54)	SOE = Moderate Serum BNP level shows moderate correlation with RAP.
BNP compared with RHC-CI	10 (550)	-0.42 (-0.54 to -0.28)	SOE = Low Serum BNP level shows negative moderate correlation with cardiac index.
BNP compared with RHC-PCWP	5 (319)	0.16 (0.01 to 0.31)	SOE = Low Serum BNP level shows poor correlation with PCWP.
BNP compared with 6MWD (absolute)	9 (484)	-0.46 (-0.55 to -0.35)	SOE = Moderate Serum BNP level shows negative moderate correlation with 6MWD.
Echocardiography-derived sPAP compared with RHC-sPAP	9 (362)	0.76 (0.53 to 0.89)	SOE = Low sPAP estimated by echocardiography shows good correlation with sPAP from RHC.

6MWD = 6-minute walk distance; BNP = B-type natriuretic peptide; CI = confidence interval; FAC = fractional area change; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; RA = right atrium; RAP = right atrial pressure; RHC = right heart catheterization; SOE = strength of evidence; sPAP=systolic pulmonary artery pressure

Table D. Summary of strength of evidence and effect estimates for the use of echocardiography or biomarkers in the prediction of mortality (KQ 2)[a]

Marker	Number of Studies (Patients)	Summary Hazard Ratio Estimate (95% CI)	SOE and Findings
BNP	6 (407)	2.42 (1.72 to 3.41)	SOE = Moderate Increase in log-transformed BNP level is a good predictor of mortality.
Pericardial effusion	8 (2,590)	2.43 (1.57 to 3.77)	SOE = Moderate Presence of pericardial effusion is a strong predictor of mortality, although there was wide variability in results for this measure.
RA size	4 (242)	1.06 (1.01 to 1.10)	SOE = Moderate RA size is a predictor of mortality.
FAC	4 (242)	0.98 (0.96 to 1.01)	SOE = Moderate FAC is a poor predictor of mortality.
Uric acid	4 (246)	1.01 (1.00 to 1.01)	SOE = Low Small increase in mortality but imprecision of estimates limit these data.
TAPSE	4 (251)	0.94 (0.82 to 1.08)	SOE = Insufficient Inconsistent results between studies lead to uncertainty.

BNP = B-type natriuretic peptide; CI = confidence interval; FAC = fractional area change; RA = right atrium; RAP = right atrial pressure; SOE = strength of evidence; TAPSE = tricuspid annular plane systolic excursion
[a]Shaded background indicates insufficient strength of evidence.

KQ 3: Pharmacotherapy for Pulmonary Arterial Hypertension

Key Points from the Results chapter are:

- In patients who have been receiving monotherapy, combination therapy appears to be moderately more effective than continuation of monotherapy for improving 6-minute walk distance (6MWD), with a magnitude of effect that is approximately equal to the estimated minimal important difference (MID) for PAH, of 6MWD of 33 meters (low strength of evidence).
- We did not identify any eligible studies that evaluated the comparative effectiveness of calcium channel blockers on intermediate-term and long-term patient outcomes, or that randomized treatment- naïve patients to monotherapy versus combination therapy, or that directly compared two drug classes.
- Although we did not intend to exclude studies of children, the inclusion criterion requiring reporting intermediate-term and long-term patient outcomes had the effect of eliminating randomized clinical trials of children with PAH.
- Prostanoids were associated with lower mortality when compared with standard therapy or placebo (low strength of evidence). Current evidence is inconclusive regarding a reduction in mortality associated with treatment with endothelin antagonists or phosphodiesterase inhibitors (insufficient strength of evidence).
- Endothelin antagonists, phosphodiesterase inhibitors, and prostanoids were all associated with improved 6MWD after 8 to 16 weeks of therapy, with a magnitude of effect that is

approximately equal to the estimated minimal important difference (MID) for PAH of 6MWD of 33 meters (moderate strength of evidence).

- Endothelin antagonists and phosphodiesterase inhibitors were associated with lower incidence of hospitalization when compared with standard therapy or placebo (moderate strength of evidence). Current evidence is inconclusive regarding a reduction in hospitalization associated with treatment with prostanoids (insufficient strength of evidence).
- Endothelin antagonists, phosphodiesterase inhibitors, and prostanoids were associated with statistically significant improvements in most or all hemodynamic measures such as PVR, mPAP, and cardiac index (low strength of evidence), compared with placebo or standard therapy. The clinical significance of the magnitude of the observed changes in these intermediate outcomes is unclear.
- Among commonly reported adverse events, there was a higher incidence of jaw pain associated with aerosolized prostanoid treatment compared with placebo (high strength of evidence) and cough associated with aerosolized prostanoids versus placebo (high strength of evidence). In addition, headache was associated with phosphodiesterase inhibitors compared with placebo or standard therapy (moderate strength of evidence), and flushing was associated with phosphodiesterase inhibitors (moderate strength of evidence) and aerosolized prostanoids (moderate strength of evidence), compared with placebo or standard therapy.

Twenty-eight RCTs involving 3,613 patients evaluated the comparative effectiveness and safety of monotherapy or combination therapy for PAH. Of these RCTs, 18 (64%) were rated good quality, 9 (32%) fair quality, and 1 (4%) poor quality. Nineteen studies (68%) were funded by industry, one by private foundation, one by government and private funding, one by private and industry funding, one by industry and "other" funding, and five did not report funding sources.

The mean patient ages ranged from 28 to 50 years old. Twenty studies enrolled patients with PAH, four studies enrolled patients with PAH associated with systemic sclerosis (formerly scleroderma), and two studies enrolled patients with Eisenmenger syndrome. Two studies enrolled a minority of patients with PH other than PAH: one included patients with chronic thromboembolic PH (28%), and another included patients with PH owing either to lung disease or to chronic thromboembolic PH (37%).

Twenty-one studies compared a single drug (monotherapy) with placebo or standard therapy and included the following drugs: bosentan (6 studies), sildenafil (2), iloprost (2), epoprostenol (3), tadalafil (3), ambrisentan (2), treprostinil (3), and vardenafil (1). For the purposes of this analysis, the standard therapy arms were grouped with the placebo arms. Standard therapies included supportive therapy (diuretics, oxygen, digoxin, oral anticoagulants) with or without calcium channel blockers, but not including newer specific vasodilator medications. One study was a head-to-head comparison of bosentan and sildenafil. The remaining five studies compared combination therapy with monotherapy: (1) intravenous (IV) epoprostenol plus bosentan versus IV epoprostenol plus placebo, (2) sildenafil plus IV epoprostenol versus IV epoprostenol plus placebo, (3) bosentan plus aerosolized iloprost versus bosentan, (4) bosentan plus aerosolized iloprost versus bosentan plus placebo, and (5) aerosolized treprostinil plus bosentan or sildenafil versus bosentan or sildenafil plus placebo. We did not identify any eligible studies published after 1990 that evaluated the safety or efficacy of calcium channel blockers on intermediate-term and long-term patient outcomes.

Most studies (85%) were multicenter trials; three were single-center trials, and four did not report the number of centers. The studies reported the following outcomes: 6MWD (27 studies), mortality (21), dyspnea (17), right heart catheterization indices (18), functional class (13), hospitalization for worsening PAH (10), quality of life (11), lung transplantation (5), right heart failure or right ventricular dysfunction (4), and brain natriuretic peptide (4). Twenty-one studies reported harms or adverse events. Table E summarizes the strength of evidence ratings for the key outcomes of mortality, 6MWD, and hospitalization. Details about the specific components of these ratings (risk of bias, consistency, directness, and precision) and information on other outcomes are available in the full report.

Table E. Summary of strength of evidence and effect estimates for monotherapy versus combination therapy for PAH (KQ 3)[a]

Intervention	Mortality	6MWD (m)	Hospitalization
Endothelin antagonist vs. placebo	SOE = Insufficient (6 studies, 838 patients) Inconclusive benefit (few studies, few deaths lead to wide CI) OR 0.60 (95% CI, 0.23 to 1.59)	SOE = Moderate (6 studies, 663 patients) Improved 6MWD with endothelin antagonists compared with placebo Mean difference 39.9 (95% CI, 21.4 to 58.4)	SOE = Moderate (3 studies, 606 patients) Reduced risk of hospitalization OR 0.34 (95% CI, 0.17 to 0.69)
Phosphodiesterase inhibitors vs. placebo	SOE = Insufficient (4 studies, 1,011 patients) Inconclusive benefit (few studies, few deaths lead to wide CI) OR 0.30 (95% CI, 0.08 to 1.11)	SOE = Moderate (4 studies, 991 patients) Improved 6MWD with PDE5 therapy compared with placebo or standard therapy Mean difference 38.9 (95% CI, 22.0 to 55.9)	SOE = Moderate (4 studies, 1,011 patients) Reduced risk of hospitalization OR 0.48 (95% CI, 0.25 to 0.91)
Prostanoids vs. placebo or standard therapy	SOE = Low (8 studies, 1,229 patients) Lower mortality with prostanoids, but inconsistent results and wide confidence intervals OR 0.52 (95% CI, 0.29 to 0.95)	SOE = Moderate (7 studies, 933 patients) Improved 6MWD with prostanoid therapy compared with placebo Mean difference 27.9 (95% CI, 10.3 to 45.4)	SOE = Insufficient (2 studies, 301 patients) Inconclusive benefit (few studies, wide CI) OR 0.42 (95% CI, 0.06 to 3.08)
Combination vs. monotherapy	SOE = Insufficient (3 studies, 566 patients) Inconclusive benefit (few studies, few deaths lead to wide CI) OR 0.37 (95% CI, 0.04 to 3.32)	SOE = Low (3 studies, 363 patients) Improved 6MWD with combination therapy compared with monotherapy Mean difference 23.9 (95% CI, 8.0 to 39.9)	SOE = Insufficient (3 studies, 566 patients) Inconclusive benefit (few studies, wide CI) OR 0.64 (95% CI, 0.31 to 1.36)

6MWD = 6-minute walk distance; CI = confidence interval; NS = not statistically significant; OR = odds ratio; SOE = strength of evidence

[a]Shaded background indicates insufficient strength of evidence.

Discussion

Key Findings and Strength of Evidence

A single study compared the combination of biomarker tests and echocardiography with echocardiography alone to screen for PAH (KKQ 1). This good-quality prospective cohort study of 372 patients suggested that biomarker testing with NT-proBNP may be useful in ruling out PAH among those suspected of PH who also have elevated sPAP by echocardiography;[24] however, this finding is limited by the lack of replication, small sample size (wide confidence limits) and confounding with RV strain on ECG. No data are available regarding combined echocardiography and biomarker screening in asymptomatic patients at high risk for PAH. In the absence of other direct comparative trials, we attempted to address this question by evaluating the efficacy of biomarker and echocardiography independently for screening and diagnosis of PAH. We reviewed 60 studies involving 7,096 patients that evaluated biomarker tests, echocardiography, or both, to screen for PAH. The associations between natriuretic peptide testing and PAH diagnosis is insufficiently strong to support its use alone as a screening test in either asymptomatic or symptomatic patients suspected of PAH. Data on biomarker testing were essentially limited to a single test—NT-proBNP—which showed moderate correlation with RHC hemodynamic measures and a great deal of variability between studies in its diagnostic accuracy and discrimination.

We found that echocardiography estimates of pulmonary artery pressures (sPAP, TG, and TRV) and pulmonary vascular resistance (TRV/VTI_{RVOT}) demonstrated good accuracy in screening for PAH. In low-prevalence populations (<10%), negative predictive value of a normal sPAP is high, suggesting that echocardiography with a low threshold may be an appropriate test in asymptomatic high-risk populations or in patients with symptoms suggesting PAH. (This is shown in studies of liver transplant patients with complete verification).

Our findings suggest that echocardiographic estimation of sPAP is sufficiently accurate to justify its role in screening for PAH in symptomatic patients suspected of having PH. However, this conclusion has several important caveats. First, echocardiography in a small but significant number of patients may not produce an estimate of sPAP because of poor-quality Doppler visualization of the tricuspid regurgitant jet. Second, echocardiographic estimates of sPAP often over- or under-estimate pulmonary artery pressure enough to result in misclassification according to PAH diagnostic threshold—hence the selection of a test threshold is critical for the aim of screening. A single test threshold is insufficient to perform with simultaneously high sensitivity and specificity (or simultaneously high positive and negative predictive values), especially in populations with higher risk or higher prevalence (more symptomatic), where echocardiography cannot be relied upon to exclude pulmonary hypertension if pretest probability is high. In asymptomatic patients at high risk for PH, echocardiography seems to perform with similar sensitivity and specificity; however, these studies suffer from verification bias, which likely inflates both the sensitivity and specificity estimates. For example, consider two prospective studies that show that approximately 10 percent of asymptomatic patients with systemic sclerosis and normal sPAP develop PH when serially retested with echocardiography. These findings are consistent with either misclassification at baseline echocardiographic screening or prospective development of PH. This ambiguity suggests that if echocardiographic screening of asymptomatic patients with a high-risk diagnosis were to be undertaken, then serial testing would be necessary.

We reviewed 99 studies, involving 8,655 patients, that evaluated biomarker tests or echocardiography to diagnose and follow progression of disease as well as response to therapy for PAH (KQ 2). Our review found that BNP showed only moderate correlation with most RHC measures (mPAP, PVR, cardiac index, RAP) and clinical measures of disease severity (6MWD) and showed weak correlation with PCWP. Most effect estimates were precise (mPAP, PVR, cardiac index, RAP, 6MWD), but estimates for PCWP were imprecise, making it difficult to interpret the clinical importance of the findings for this measure. For the other measures, correlation with BNP was moderate, indicating that BNP levels alone could not serve as an accurate surrogate marker for disease severity. Alternatively, echocardiography-derived sPAP showed strong correlation with RHC-sPAP with a precise effect estimate, and may be useful as an alternative to RHC to assess disease severity. However, there was a great deal of heterogeneity among these studies.

BNP level and the presence of pericardial effusion were predictors of mortality and may be useful clinically, though results were not highly precise. RA size and uric acid were also associated with mortality, but studies were less consistent than for BNP. FAC showed no significant ability to predict mortality; data on TAPSE were too inconsistent to be conclusive.

Our findings do not support any recommendations for replacing existing measurement tools to assess disease severity, prognosis, or response to therapy. Echocardiography-derived sPAP shows promise as a possible surrogate marker for RHC-sPAP, but it is unclear whether or not this measure alone is adequate to assess disease severity, prognosis, or response to therapy.

We reviewed 37 studies involving 4,192 patients that assess the effectiveness of drug treatment for PAH in adults. Our review found inconclusive evidence regarding mortality reduction for 11 of the 12 drug treatment comparisons: (1) ambrisentan versus placebo (OR 0.40; 95% CI, 0.10 to 1.51), (2) bosentan versus placebo (OR 0.72; CI, 0.14 to 3.60). (3) epoprostenol versus placebo or standard therapy (OR 0.33; CI, 0.07 to 1.50), (4) iloprost versus placebo (OR 0.43; CI, 0.08 to 2.47), (5) sildenafil versus placebo (OR 1.01; CI, 0.10 to 9.92), (6) tadalafil versus placebo (OR 0.50; CI, 0.05 to 5.63), (7) treprostinil versus placebo (OR 0.50; CI, 0.12 to 2.12), (8) vardenafil versus placebo (OR 0.08; CI, 0.00 to 1.82), (9) endothelin antagonists versus placebo (OR 0.60; CI, 0.23 to 1.59), (10) phosphodiesterase inhibitors versus placebo (OR 0.30; CI, 0.08 to 1.11), and (11) combination therapy versus monotherapy (OR 0.37; CI, 0.04 to 3.32).

Few deaths were observed in these limited-duration studies, leading to wide confidence intervals and lack of statistical power to detect a difference in mortality; however, a consistent direction of effect and demonstrated improvements in other outcomes, including functional and hemodynamic measures, support that a mortality reduction might exist.

Increases in 6MWD ranging from 27.9 meters (95% CI, 10.3 to 45.4) to 39.9 meters (CI, 21.4 to 58.4) were observed in trials of all drug classes when compared with placebo or standard therapy; however, comparisons between agents are inconclusive. The magnitude of these statistically significant improvements in 6MWD associated with treatment are very close to a recently published estimate of 33 meters for the minimal important difference for the 6MWD in patients with PAH.[25] Combination therapy in patients already on monotherapy also showed improved 6MWD compared with continuation of monotherapy (OR 23.9; CI, 8.0 to 39.9), but the diversity of treatment regimens and the small number of combination therapy trials again make comparisons between specific regimens inconclusive. In studies evaluating hospitalization, endothelin receptor antagonists and phosphodiesterase-5 inhibitor treatment was associated with lower odds of hospitalization compared with placebo (OR 0.34 and 0.48, respectively). The

magnitude of the odds ratio associated with prostanoids was similar (OR 0.42), but the 95% confidence interval included 1.0, thereby making this finding not statistically significant. Combination therapy compared with monotherapy also showed a similar nonsignificant effect on hospitalizations (OR 0.64). Endothelin antagonists, phosphodiesterase inhibitors, and prostanoids each had favorable effects on most hemodynamic outcomes including cardiac index, mPAP, and PVR.

In studies reporting adverse effects, we found that phosphodiesterase-5 inhibitors were more likely than endothelin receptor antagonists to cause headache, and endothelin antagonists still were more likely than placebo to cause headache. Drugs did not significantly differ in their odds of causing dizziness or diarrhea. Aerosolized prostanoids were much more likely to cause jaw pain and cough compared with placebo. Phosphodiesterase-5 inhibitors and prostanoids were associated with flushing, while data on endothelin receptor antagonists were inconclusive. Phosphodiesterase-5 inhibitors had a significant association with peripheral edema, while data on prostanoids and endothelin receptor antagonists were inconclusive.

The findings from our meta-analyses of the few studies that compared combination therapy with monotherapy suggest, but do not prove, that combination therapy confers more benefit than does monotherapy in the treatment of PAH. These findings are generally consistent with the European Society of Cardiology (ESC)/European Respiratory Society (ERS) guideline recommendation for monotherapy as initial treatment, with combination treatment reserved for patients who have an inadequate clinical response to monotherapy.

Applicability

The principal limitations to applicability of data on the diagnosis of PAH all relate to the patient populations studied. First, the studies may not be applicable to the screening of asymptomatic patients. None of the study populations consisted entirely of asymptomatic patients, and although many studies included some patients without symptoms, they were not reported separately in terms of outcomes. Some studies of populations in whom PAH was suspected failed to adequately describe the basis for a clinical suspicion of PAH, whether symptoms of dyspnea, clinical signs, or other test results, such as diffusion capacity of the lung for carbon monoxide (DLCO), thus the applicability of these studies for screening symptomatic patients was also limited.

A second kind of limitation resulted from the fact that the spectrum of disease among study populations was often skewed, particularly in case-control studies, by selection criteria that selected from patients with known PAH (cases) and patients known not to have PAH (controls). Such studies usually excluded participants with other conditions that might be confused with PAH such as PH due to left-sided heart failure, thrombotic disease, or chronic obstructive pulmonary disease.

A third limitation was that participants in many studies had a wide range of disease severity, particularly those cases in case-control design studies, making these studies a poor match for the question at hand. Other applicability issues identified in the KQ 1 studies were less frequent and judged to be less severe.

Our findings in KQ 2 assessing the prognostic or predictive value of biomarkers and echocardiography may not be applicable to all PAH populations. The greatest concern is that studies reviewed in KQ 2 included participants at widely differing points in the natural history of disease, who had widely differing degrees of disease severity and different underlying etiologies of PAH. There was also concern that the population was not adequately described to assess

applicability, included patients with conditions other than PAH, or in general did not match the review question. Applicability may also be limited by the use of surrogate markers that may not be clinically relevant; also by insufficient followup time. In a few studies, it was also felt that the intervention arm or cointerventions did not adequately reflect current clinical practice or that the study setting was widely divergent from the current typical U.S. setting. Finally, there is concern that some studies did not provide adequate information about adverse events.

Applicability considerations were somewhat different for KQ 3 than for the KQs about screening and management of PAH. Most of the studies included in this review for KQ 3 were RCTs with generally good internal validity. Patient populations, however, differed between studies; variation in eligibility criteria resulted in differences between study populations in severity of illness, underlying etiology of PAH, comorbid conditions, and prior and concurrent treatment. Many different countries were represented, thereby introducing potential differences in clinical practice and care delivery settings relative to current practice in typical settings in the United States. There was also concern that the population was not always adequately described to assess applicability, with few studies exploring potential differences in response to treatment among different patient subgroups. Finally, the studies that compared combination therapy with monotherapy were all of similar design, randomizing patients who had previously received monotherapy to either continued monotherapy with that drug or continued therapy with that drug plus the addition of a second drug. While we considered these studies to represent a comparison of combination therapy with monotherapy, we do so with the understanding that this study design does not address the question of whether initiating two drugs is superior to initiating a single drug to treatment-naïve patients.

Research Gaps

The available evidence leaves numerous gaps and areas for potential future research. We used the framework recommended by Robinson et al.[26] to identify gaps in evidence and describe why these gaps exist. Results are as follows:

KQ 1: Screening for PAH

- Patients at elevated risk for PAH, other than those with systemic sclerosis, have seldom been studied in screening test studies.
    - Consider cohort studies of testing for PH among high-risk populations other than those with systemic sclerosis; including patients with HIV, sickle cell anemia or trait portal hypertension, family history of PAH, or catecholaminergic drug use.
    - Different populations may have different risks of PAH and different benefits from screening; in studies where heterogeneous populations are included, the effectiveness of screening should be examined according to risk factor.
- Relatively few data exist on screening of asymptomatic patients with a combination of echocardiography and biomarker testing.
    - Consider cohort studies that apply echocardiography and biomarker screening in a coordinated or algorithmic way, and studies that verify diagnosis in at least a sample of test-negative patients by RHC or lengthy followup.
    - Future tests of the added value of biomarkers should use well validated echocardiography parameters as a screening test, including estimates of pulmonary artery pressures (sPAP, TG, and TRV) and pulmonary vascular resistance (TRV/VTI_{RVOT}).

- Studies of echocardiography for diagnosis of PH have focused on the association of single measures or parameters at a time rather than an integrated diagnostic assessment based on an entire examination and multiple echocardiographic measures or parameters.
    - Consider studies that evaluate a global echocardiographic assessment based not only on sPAP but also on right heart chamber size wall thickness and function, estimated PVR, and left heart measures.
    - Consider further development of data on the use of echocardiography to measure exercise response to sPAP.
    - Consider further development of echocardiographic estimation of mPAP, which would better align with the diagnostic criteria for PAH.
    - Consider studies of additional promising measures such as end diastolic pulmonary regurgitation gradient, mean tricuspid regurgitation gradient, and Doppler tissue imaging of the tricuspid annulus.

KQ 2: Management of PAH

- Echocardiographically guided and BNP-guided treatment strategies have not been explicitly tested.
    - Consider cohort studies evaluating prognosis, as well as treatment trials examining association of baseline echocardiographic parameters and BNP levels with response to treatment.
- Other imaging modalities, such as magnetic resonance imaging, have been little studied as alternative noninvasive tests to assess RV function.
- Cardiopulmonary exercise testing and exercise echocardiography have yielded relatively few data, and their clinical utility and relationship to PH diagnostic criteria are uncertain.
    - Consider validation studies to demonstrate prognostic value, particularly for patients with normal resting echocardiography but abnormal exercise echocardiography.

KQ 3: Pharmacotherapy for PAH

- Relatively few data exist on the efficacy of treating PAH early in the disease course (WHO functional class I-II).
    - Improved data on efficacy of early PAH treatment would strengthen linkage to data on efficacy of screening testing.
    - Consider treatment trials in early-stage PAH, particularly among patients identified by case finding or screening interventions.
- Relatively few data exist on children with persistent PH or congenital heart disease.
    - Consider controlled trials in children.
- Few treatment trials address direct comparison of alternative drug treatments, particularly for PAH patients early in the disease course.
    - Consider trials designed to compare clinical alternative treatments to permit more evidence-based treatment selection, such as head-to-head treatment comparisons rather than placebo-control, or combination versus monotherapy trials.
- The majority of RCTs have been too short and small to generate definitive data on major patient-centered outcomes. Although surrogate markers have limitations, more complete collection, analysis, and correlation of these markers with patient-centered outcomes may not only help to validate surrogate outcomes but also provide more practical outcome measures.

    - Consider including biomarker and imaging techniques with conventional clinical outcomes to improve data on validity and responsiveness of surrogate outcomes.
- Few data are available from trials about differences in response to treatment based on patient characteristics.
    - Consider subgroup analysis of treatment efficacy by WHO functional class, underlying etiology, and other patient-level factors.
- Data on the efficacy of combination treatments are limited.
    - Consider more combination treatment trials, in particular trials with clear criteria for starting combination therapy, and trials in patients who have not failed monotherapy.
- The duration of controlled trial efficacy data are limited.
    - Consider, particularly for clinically relevant comparisons (e.g., head-to-head treatment or combo versus monotherapy trials), longer term followup studies that retain randomized group comparisons while assessing long-term efficacy.

Conclusions

Further research is needed to confirm the single good-quality study suggesting that echocardiography and the biomarker NT-proBNP in combination may be sufficiently accurate to rule out PAH when testing symptomatic patients. In asymptomatic populations, more research is needed to draw conclusions regarding the effectiveness for screening. BNP, RA size, the presence of pericardial effusion and uric acid had prognostic value in patients with PAH, but other echocardiographic parameters and biomarkers either were not predictive or had insufficient data. Although no treatments demonstrate a strong and consistent mortality reduction, many are associated with improved 6MWD and reduced hospitalization rates. Comparisons of different drug combinations are inconclusive regarding mortality reduction but suggest an improvement in 6MWD compared with continuation of monotherapy.

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Glossary

6MWD	6-minute walk distance
AHRQ	Agency for Healthcare Research and Quality
BID	two times per day
BNP	B-type natriuretic peptide
CI	confidence interval
CHF	congestive heart failure
COPD	chronic obstructive pulmonary disease
CTEPH	chronic thromboembolic pulmonary hypertension
CVD	collagen vascular disease
FAC	fractional area change
FC	functional class
HR	hazard ratio
HRQOL	health-related quality of life
IQR	interquartile range
KQ	Key Question
MI	myocardial infarction
mo	month/months
mPAP	mean pulmonary artery pressure
MPI	myocardial performance index
NA	not applicable
NR	not reported
NT-proBNP	N-terminal pro-B-type natriuretic peptide
OR	odds ratio
PAH	pulmonary arterial hypertension
PADP	pulmonary artery diastolic pressure
PASP	pulmonary artery systolic pressure
PCWP	pulmonary capillary wedge pressure
PH	pulmonary hypertension
PPH	primary pulmonary hypertension
PVR	pulmonary vascular resistance
QOL	quality of life
RA	right atrium
RAP	right atrial pressure
RHC	right heart catheterization
RIMP	right index of myocardial performance
RR	risk ratio
RV	right ventricle
RVEF	right ventricle ejection fraction
SD	standard deviation
SEM	standard error of the mean
SOE	strength of evidence
sPAP	systolic pulmonary artery pressure
SSc	systemic sclerosis
TAPSE	tricuspid annular plane systolic excursion

TEP	Technical Expert Panel
TRV	tricuspid regurgitant jet velocity
VSD	ventricular septal defect
VTI_{RVOT}	velocity-time integral of right ventricular outflow tract
yr	year/years

Introduction

Background

Epidemiology and Etiology of Pulmonary Arterial Hypertension

Pulmonary arterial hypertension (PAH), a subcategory of pulmonary hypertension (PH), is a rare and progressive disease whose prevalence is estimated to be between 15 and 50 cases per million adults.[1] While the pathophysiology is not well understood, both genetic and environmental factors have been found to contribute to changes in the pulmonary vasculature, causing increased pulmonary vascular resistance. This increased resistance, if unrelieved, progresses to right ventricular pressure overload, dysfunction, and ultimately right heart failure and premature death.[2] The causes of PAH are numerous and are listed in Table 1, taken from the Fourth World Symposium on PAH (2008).[3] Before the availability of disease-specific therapy in the mid-1980s, the median life expectancy at the time of diagnosis was 2.8 years.[1,4]

Table 1. Updated clinical classification of pulmonary hypertension (Dana Point, 2008)[a]

1.	**Pulmonary arterial hypertension (PAH)**
1.1	Idiopathic PAH
1.2	Heritable
1.2.1	BMPR2
1.2.2	ALK1, endoglin (with or without hereditary hemorrhagic telangiectasia)
1.2.3	Unknown
1.3	Drug and toxin-induced
1.4	Associated with:
1.4.1	Connective tissue disease
1.4.2	HIV infection
1.4.3	Portal hypertension
1.4.4	Congenital heart diseases
1.4.5	Schistosomiasis
1.4.6	Chronic hemolytic anemia
1.5	Persistent pulmonary hypertension of the newborn
1'.	**Pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH)**
2.	**Pulmonary hypertension owing to left heart disease**
2.1	Systolic dysfunction
2.2	Diastolic dysfunction
2.3	Valvular disease
3.	**Pulmonary hypertension owing to lung diseases and/or hypoxemia**
3.1	Chronic obstructive pulmonary disease
3.2	Interstitial lung disease
3.3	Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4	Sleep-disordered breathing
3.5	Alveolar hypoventilation disorders
3.6	Chronic exposure to high altitude
3.7	Developmental abnormalities
4.	**Chronic thromboembolic pulmonary hypertension (CTEPH)**
5.	**Pulmonary hypertension with unclear multifactorial mechanisms**
5.1	Hematologic disorders: myeloproliferative disorders, splenectomy
5.2	Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis: lymphangioleiomyomatosis, neurofibromatosis, vasculitis

Table 1. Updated clinical classification of pulmonary hypertension (Dana Point, 2008)[a] (continued)

5.3	Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4	Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

[a] Fourth World Symposium on PAH in Dana Point, CA (2008).

Table reprinted from the Journal of the American College of Cardiology, Vol 54, No. 1, Suppl S, Simonneau G, Robbins IM, Beghetti M, et al., Updated Clinical Classification of Pulmonary Hypertension, Pages No. S43-54, Copyright 2009, with permission from Elsevier.[3]

Screening and Diagnosis

There are two separate populations where screening for PAH needs to be considered. First, there are patients with symptoms that raise the suspicion of PAH. The symptoms of PAH can be insidious and nonspecific and may include shortness of breath, fatigue, weakness, chest pain, syncope, leg swelling and abdominal distention. Symptoms that are present at rest suggest advanced disease.[1] Since these symptoms are nonspecific, screening may be necessary to help decide whether the patient should undergo a diagnostic workup for PAH, or whether other conditions should be considered. The other population is patients with medical conditions that put them at risk for PAH. In these patients screening tests may be used to identify patients with asymptomatic elevation of pulmonary artery pressures, who might be more closely monitored for the development of symptoms or progressive disease or offered a diagnostic workup for PAH, and possibly treatment for early disease.

Once screening indicates the possibility of PAH, diagnostic tests are necessary to confirm the presence of elevated right-sided heart pressures and to exclude valvular, primary myocardial, chronic lung disease, thromboembolic, and miscellaneous other causes of pulmonary hypertension (PH). The reference standard for diagnosing PAH is right heart catheterization (RHC), which is invasive but generally safe. In a retrospective and prospective study by Hoeper et al.,[5] the rate of serious complications in patients undergoing RHCs for evaluation of pulmonary hypertension was 1.1 percent and included bleeding, vasovagal reactions, systemic hypotension, arterial injury, hypertensive crisis, pneumothorax, and cardiac arrhythmias. The procedure-related mortality was 0.055 percent.[5]

RHC not only confirms the diagnosis of PAH but also provides prognostic hemodynamic information (mean right atrial pressure, pulmonary vascular resistance)[6] to direct treatment decisions. A small subset of patients with PAH, when challenged with a short-acting pulmonary vasodilator, will experience a drop in mean pulmonary artery pressure of at least 10 mmHg (20%) to below 40 mmHg while maintaining cardiac output; this predicts a favorable long-term response to calcium channel blockers.[1]

Since PAH is a progressive disease, regular reassessment is needed to monitor response to treatment and adjust prognosis. RHC has traditionally been the means by which patients' clinical course is monitored; however, transthoracic echocardiography has emerged as a possible alternative because of its availability, safety, and cost. The number of echocardiographic modalities has increased substantially, providing unique insight into the structure and function of the right heart in patients with pulmonary hypertension.[7] However, this test has not been definitively validated as a substitute for RHC in patients with PAH. Finally, the role of biomarkers has not been fully established in the management and prognosis of PAH. Defining whether biomarkers alone or biomarkers plus echocardiography might be superior to echocardiography alone for informing treatment decisions is a necessary first step in establishing a noninvasive, multifaceted approach to the management of PAH.

Role of Echocardiography

The role of echocardiography in the diagnosis and management of patients with PAH has evolved over time, and has been proposed for screening, assessing prognosis, and evaluating response to treatment. Screening high-risk individuals for PAH generally begins with a transthoracic echocardiogram.[8] Echocardiography can estimate the right ventricular systolic pressure and identify other signs of PH including increased right-sided chamber size and wall thickness. Most often, the peak velocity of the tricuspid regurgitant (TR) jet is measured by Doppler and—along with an estimate of right atrial pressure based on inspiratory collapse and size of the inferior vena cava—TR jet is used to estimate the systolic pulmonary artery pressure (sPAP). However, a significant proportion of patients have no measureable TR jet. Estimates are often inaccurate compared with RHC; up to 60 percent of echocardiography estimates were more than 10 mmHg off from RHC measurements in one large multicenter registry of PAH patients.[9] Furthermore, sPAP is dependent on right ventricle (RV) systolic function and stroke volume. In later stages of PH, RV function deteriorates, which can lessen the degree of sPAP elevation and lead to an underestimate of pulmonary vascular resistance (PVR). More recent echocardiographic-based methods have focused on evaluating RV systolic function. Therefore, although transthoracic echocardiography is the standard screening test for PAH, it is less than completely accurate and there is uncertainty as to which echocardiographic measurements are most useful.

Several studies have investigated the use of echocardiography in establishing prognosis in PAH. In a study of patients with systemic sclerosis (n=155), calculation of the right ventricular systolic pressure (RVSP) using Doppler echocardiography identified 47 patients (36.4%) with RVSP ≥36 mmHg who had decreased 3-year survival rates compared with patients with RVSP <36 mmHg (67% versus 86%, $p < 0.01$).[10] Another study of patients with PAH (n=80) using echocardiography to calculate right ventricular free wall strain found that patients with strain worse than -12.5 percent were associated with increased 6-month disease progression and increased mortality at 1 year (unadjusted hazard ratio 6.2).[11] There remains uncertainty regarding which echocardiographic measure(s) have prognostic value although tricuspid annular plane systolic excursion (TAPSE) and pericardial effusion have been proposed.[12] Traditionally, RHC assessment of hemodynamics is recommended to demonstrate treatment response;[12] echocardiography has been seldom studied in this role.

Role of Biomarkers

Because of the limitations of echocardiography, the potential role of biomarkers in screening for and managing of PAH has been the subject of increasing interest over the last decade. Brain natriuretic peptide (BNP) and N-terminal BNP (NT-proBNP) are two biological substances found in the blood that have been studied as a screening test in patients at risk for PAH and which have been shown to correlate well with the presence of disease.[13,14] Other biomarkers currently under investigation include atrial natriuretic peptide, endothelin-1, uric acid, troponin T, nitric oxide, asymmetric dimethylarginine, cyclic guanosine monophosphate, D-dimer, and serotonin. Several of these biomarkers have been shown to correlate with prognosis and mortality, either alone or in conjunction with other traditional measurements such as the 6-minute walk distance (6MWD) test, functional class assessment, and pulmonary hemodynamics.[15] Select biomarkers may even be superior to traditional testing. Patients with idiopathic and familial PAH were shown to exhibit dysregulation over a broad range of inflammatory cytokines, such as tumor necrosis factor-alpha and interleukin-6, when compared

with healthy controls, which correlated better with prognosis than 6MWD and pulmonary hemodynamics.[16]

Treatment Strategies

Medications

The goal of medical treatment for PAH is both to improve patients' symptomatic status and to slow the rate of clinical deterioration. In addition to supportive therapy (diuretics, oxygen, digoxin, oral anticoagulants), specific drug therapy is recommended. There has been rapid development and approval of vasodilator medications for PAH over the past three decades. Currently, there are four main classes of medications used to treat PAH, as shown in the bulleted list below.[17] Calcium channel blockers are indicated for the minority of patients who have positive acute vasoreactivity testing and demonstrate a sustained response. Most patients are candidates for treatment with one of the other three classes of medications.

- Calcium channel blockers:
    - Amlodipine
    - Diltiazem
    - Nifedipine
- Prostacyclin analogues:
    - Epoprostenol
    - Iloprost
    - Treprostinil
- Endothelin receptor antagonists:
    - Bosentan
    - Ambrisentan
- Phosphodiesterase type 5 inhibitors:
    - Sildenafil
    - Tadalafil

These PAH medications have been shown to improve dyspnea, 6MWD, pulmonary hemodynamics, and functional class. Calcium channel blockers are associated with long-term (>1 year) improvements in hemodynamics and functional status in most of those patients who show acute vasoreactivity testing response; however, acute vasoreactivity is seen in a minority of patients tested.[18] The limited usefulness of calcium antagonists—as well as the poor prognosis and diminished quality of life associated with PAH—reinforces the need for new drug therapies and improved delivery of current medications. Limited data suggest that epoprostenol and bosentan may provide a survival benefit; however, this end point has not been studied consistently between the medications.[19] The three medications most recently approved by the U.S. Food and Drug Administration for PAH are: (1) inhaled treprostinil, a new delivery system for this prostacyclin analogue, (2) tadalafil, a new phosphodiesterase type 5 inhibitor, and (3) ambrisentan, an endothelin receptor antagonist. With the exception of tadalafil, these new medications were discussed in the Expert Consensus Document on Pulmonary Hypertension released in 2009 by the American College of Cardiology Foundation and the American Heart Association.[19] Since then, however, numerous studies have been published regarding the safety and efficacy of these new medications. Also, more data have been published on the older medications for PAH. These new data may clarify any effect on mortality and gauge the comparative effectiveness of these drugs.

Additionally, combination drug therapy (using multiple drugs with different mechanisms of action) is an important area of research and may be the most promising way to improve clinical outcomes although at higher cost.[2] Combination therapy was addressed in the 2009 ACCF/AHA publication, and several studies have since been published on this topic. In order to optimize PAH care, newer information regarding the latest drugs and combination therapies should be systematically reviewed.[17]

Scope and Key Questions

Scope of the Review

This comparative effectiveness review was funded by the Agency for Healthcare Research and Quality (AHRQ). It was designed to evaluate the comparative validity, reliability, and feasibility of echocardiography and biomarker testing for the diagnosis and management of PAH in addition to clarifying whether the use of echocardiography and biomarkers affects decisionmaking and clinical outcomes. We also wanted to address which medications are effective for treating PAH and how the newer medications compare with older ones and with each other. Further, there was a need for clarity about whether combination therapy is more effective than monotherapy and what effect monotherapy or combination therapy has on intermediate-term and long-term outcomes.

Key Questions

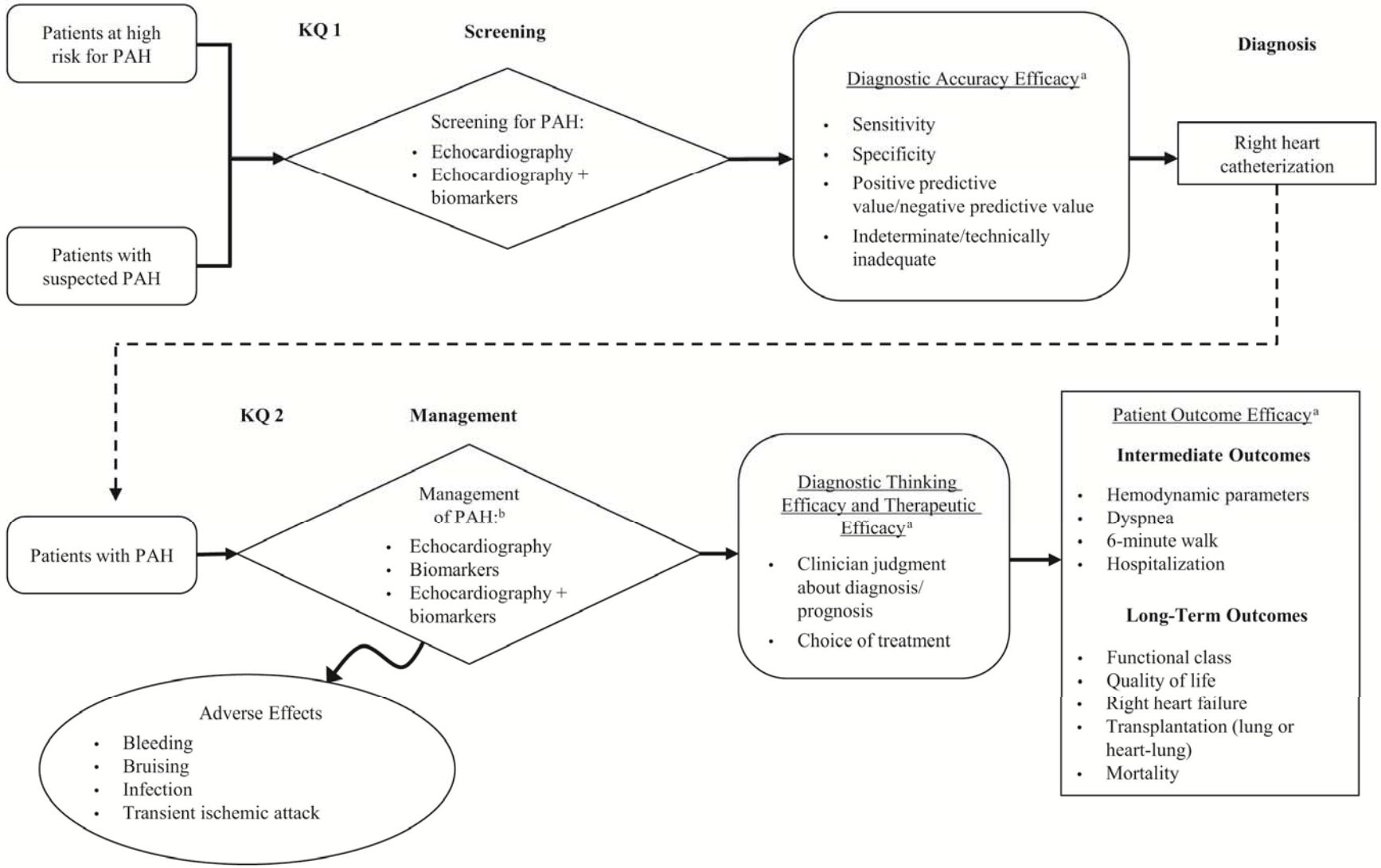
With input from our Key Informants, we constructed Key Questions (KQs) using the general approach of specifying the population of interest, the interventions, comparators, outcomes, timing of outcomes, and settings (PICOTS; see the section on "Inclusion and Exclusion Criteria" in the Methods section for details). The KQs considered in this comparative effectiveness review were:

- KQ 1: For patients with suspected pulmonary arterial hypertension (PAH) and asymptomatic patients at high risk for PAH, what is the comparative effectiveness and safety of echocardiography versus echocardiography plus biomarkers as screening modalities before right heart catheterization to establish the diagnosis of PAH (diagnostic accuracy efficacy)?
- KQ 2: For patients with PAH, what is the comparative effectiveness and safety of (a) echocardiography versus biomarkers and (b) echocardiography versus echocardiography plus biomarkers in managing PAH and on intermediate-term (≤90 days) and long-term (>90 days) patient outcomes?
- KQ 3: For patients with PAH, what is the comparative effectiveness and safety of monotherapy or combination therapy for PAH using calcium channel blockers, prostanoids, endothelin receptor antagonists, or phosphodiesterase inhibitors on intermediate-term and long-term patient outcomes?

Analytic Framework

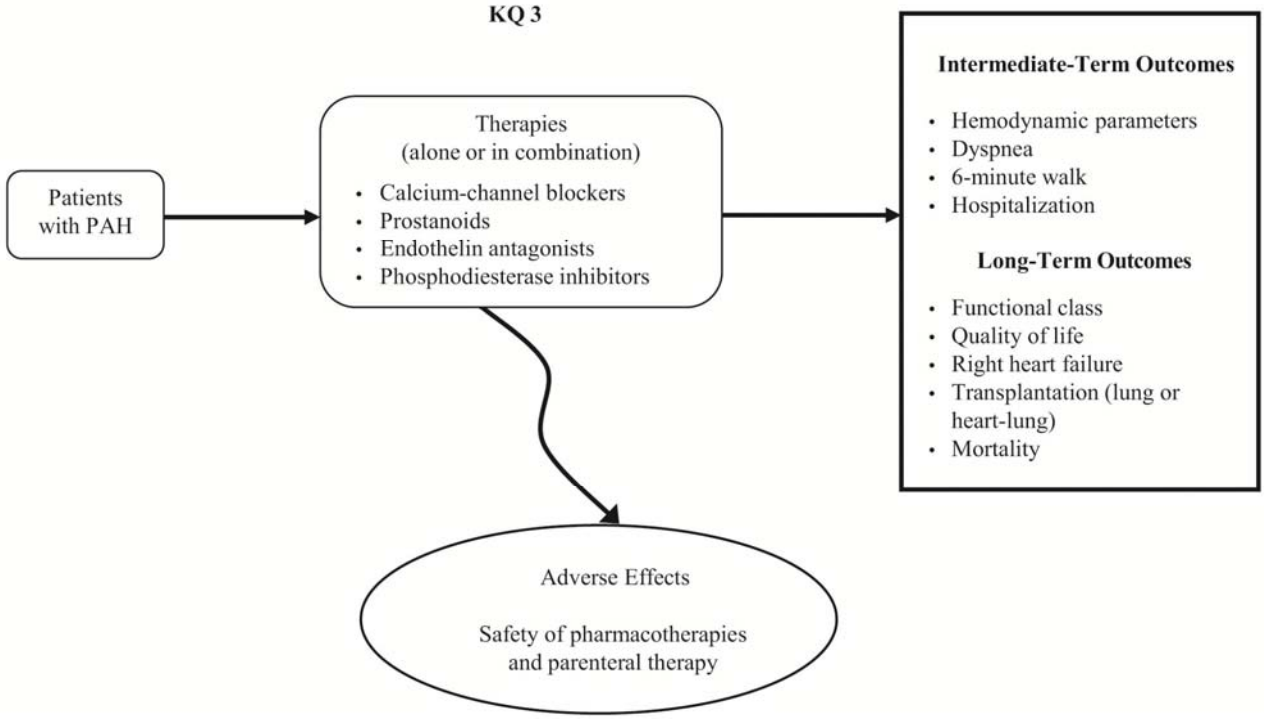
Figures 1 and 2 show the analytic framework for this comparative effectiveness review.

Figure 1. Analytic framework for KQs 1 and 2



KQ = Key Question; PAH = pulmonary arterial hypertension
[a]Fryback DG, Thornbury JR. The efficacy of diagnostic imaging. Med Decis Making 1991;11(2):88-94.
[b]In conjunction with routine clinical assessment (functional class, dyspnea, 6-minute walk).

Figure 2. Analytic framework for KQ 3



KQ = Key Question; PAH = pulmonary arterial hypertension

Methods

The methods for this comparative effectiveness review follow those suggested in the AHRQ "Methods Guide for Effectiveness and Comparative Effectiveness Reviews" (available at www.effectivehealthcare.ahrq.gov/methodsguide.cfm; hereafter referred to as the Methods Guide).[20] The main sections in this chapter reflect the elements of the protocol established for the systematic review; certain methods map to the PRISMA checklist.[21] All methods and analyses were determined a priori.

Topic Refinement and Review Protocol

During the topic refinement stage, we solicited input from Key Informants representing clinicians (pulmonology, cardiology, pathology), patients, scientific experts, and Federal agencies, to help define the Key Questions. The Key Questions were then posted for public comment for 30 days, and the comments received were considered in the development of the research protocol. We next convened a Technical Expert Panel (TEP), comprising clinical, content, and methodological experts, to provide input in defining populations, interventions, comparisons, or outcomes as well as identifying particular studies or databases to search. The Key Informants and members of the TEP were required to disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Any potential conflicts of interest were balanced or mitigated. Neither Key Informants nor members of the TEP did analysis of any kind and did not contribute to the writing of the report. Members of the TEP were invited to provide feedback on an initial draft of the review protocol, which was then refined based on their input, reviewed by AHRQ, and posted for public access at the AHRQ Effective Health Care Web site.[22]

Literature Search Strategy

Sources Searched

Our search strategy used the National Library of Medicine's medical subject headings (MeSH) keyword nomenclature developed for MEDLINE® and adapted for use in other databases. In consultation with our research librarians, we searched PubMed®, Embase®, and the Cochrane Database of Systematic Reviews (Appendix A). We limited the search to English-language studies conducted from 1995 to the present for KQs 1 and 2, and 1990 to the present for KQ 3; prior to 1990, newer drug treatments were not available, and prior to 1995 older echocardiographic and biomarker testing technology is less applicable. Where possible, we used existing validated search filters (such as the Clinical Queries Filters in PubMed®). We supplemented the electronic searches with a manual search of citations from a set of key primary and review articles. The reference list for identified pivotal articles was hand-searched and cross-referenced against our library, and additional manuscripts were retrieved. All citations were imported into an electronic database (EndNote® X4; Thomson Reuters, Philadelphia, PA).

We also searched the gray literature of study registries and conference abstracts for relevant articles from completed studies. Gray literature databases included ClinicalTrials.gov; metaRegister of Controlled Trials; ClinicalStudyResults.org; WHO: International Clinical Trials Registry Platform Search Portal; and ProQuest COS Conference Papers Index. Scientific information packets were requested from the manufacturers of medications and devices and

reviewed for relevant articles from completed studies not previously identified in the literature searches.

Although this was not an exhaustive strategy, the search of ClinicalTrials.gov was also used as a mechanism to ascertain publication bias by identifying completed but unpublished studies. During peer and public review of the draft report, we updated all database searches and included any eligible studies identified either through that search or through suggestions from peer and public reviewers.

Inclusion and Exclusion Criteria

The PICOTS criteria used to screen articles for inclusion/exclusion at both the title-and-abstract and full-text screening stages are detailed in Table 2.

Table 2. Inclusion and exclusion criteria

Study Characteristic	Inclusion Criteria	Exclusion Criteria
Population	• KQ 1: Patients with suspected pulmonary arterial hypertension (PAH) or asymptomatic patients at high risk for PAH (e.g., patients with a collagen vascular disorder such as scleroderma) • KQs 2 and 3: Patients with PAH	KQ 1: Patients have neither (1) a condition associated with a high risk of undiagnosed PAH (e.g., a collagen vascular disorder) nor (2) signs or symptoms suspicious for PAH KQ 2 and KQ 3: No patients have PAH
Interventions	• KQ 1 (screening): Echocardiography plus biomarkers including natriuretic peptides (e.g., atrial natriuretic peptide, brain natriuretic peptide), endothelin-1, uric acid, troponin T, nitric oxide, asymmetric dimethylarginine, cyclic guanosine monophosphate, D-dimer, and serotonin • KQ 2 (management): o Biomarkers plus clinical assessment (e.g., history, physical exam, functional status) o Echocardiography plus biomarkers plus clinical assessment • KQ 3 (pharmacotherapies): o Calcium channel blockers (amlodipine, diltiazem, nifedipine, verapamil) o Prostanoids (epoprostenol, treprostinil, iloprost) o Endothelin antagonists (bosentan, ambrisentan) o Phosphodiesterase inhibitors (sildenafil, tadalafil)	Study does not include a comparison of echocardiography or biomarkers for screening, diagnosis, or management of PAH, or does not include a comparison of monotherapy with combination therapy for PAH

Table 2. Inclusion and exclusion criteria (continued)

Study Characteristic	Inclusion Criteria	Exclusion Criteria
Comparators	• KQ 1: Echocardiography vs. echocardiography plus biomarkers • KQ 2: o Echocardiography vs. biomarkers (direct comparison) o Echocardiography vs. echocardiography plus biomarkers (direct comparison) o Echocardiography vs. clinical assessment (indirect comparison) o Biomarkers vs. clinical assessment (indirect comparison) • KQ 3: o One pharmacotherapy vs. another pharmacotherapy o Monotherapy vs. combination therapy	Study does not include a comparison of echocardiography or biomarkers for screening, diagnosis, or management of PAH, or does not include a comparison of monotherapy with combination therapy for PAH
Outcomes	• KQ 1: Test-associated outcomes: Diagnostic accuracy efficacy (sensitivity, specificity, positive predictive value/negative predictive value); verification by right heart catheterization for test positive patients was required (incomplete verification of test negative patients was allowed) • KQ 2: Efficacy outcomes: o Diagnostic thinking efficacy and therapeutic efficacy (clinician judgment about diagnosis/prognosis, choice of treatment) o Patient outcome efficacy for intermediate-term outcomes (hemodynamic parameters, dyspnea, and 6-minute walk) and long-term outcomes (functional class, quality of life, right heart failure, and mortality) • KQ 3: Effectiveness of pharmacotherapies: o Intermediate-term outcomes such as hemodynamic parameters, dyspnea, and 6-minute walk o Long-term outcomes such as functional class, quality of life, right heart failure or right ventricular dysfunction, and mortality	No primary or secondary outcomes of interest are reported
Outcomes (safety)	• KQs 1 and 2: Adverse effects of echocardiography and biomarkers, such as bleeding, bruising, infection, and transient ischemic attack • KQ 3: Adverse effects of pharmacotherapies (liver function abnormalities, headache, flushing, cough, epistaxis, dyspepsia, diarrhea, peripheral edema, nausea, nasal congestion, dizziness, syncope, hypoxia, increased international normalized ratio or prothrombin time) and parenteral therapy (line infection, site pain, abrupt catheter occlusion)	None
Timing	Intermediate-term (≤120 days) and long-term (>120 days)	None

Table 2. Inclusion and exclusion criteria (continued)

Study Characteristic	Inclusion Criteria	Exclusion Criteria
Setting	• Inpatient and outpatient • Specialty (pulmonary, cardiology, rheumatology) and primary care	None
Study design	• Randomized controlled trial, prospective or retrospective observational study, or registry • Original data (or related methodology paper of an included article) for any of the screening or diagnostic tests listed in the KQs, or original data with intermediate-term or long-term outcomes associated with monotherapy or combination therapy for PAH • Relevant systematic review or meta-analysis (used for background only) • All sample sizes	Not a clinical study (e.g., editorial, nonsystematic review, letter to the editor, case series)
Publications	• English-language only • Peer-reviewed article • KQs 1 and 2: Published January 1, 1995, to present • KQ 3: Published January 1, 1990, to present	Given the high volume of literature available in English-language publications (including the majority of known important studies), non-English articles are excluded[b]

KQ = Key Question; PAH = pulmonary arterial hypertension

Study Selection

Using the prespecified inclusion and exclusion criteria, titles and abstracts were examined independently by two reviewers for potential relevance to the Key Questions. Articles included by any reviewer underwent full-text screening. At the full-text screening stage, paired researchers independently reviewed the articles and indicated a decision to include or exclude the article for data abstraction. When the paired reviewers arrived at different decisions, we reconciled the difference through review and discussion or through a third-party arbitrator, if needed. Articles meeting eligibility criteria were included for data abstraction. Relevant systematic review articles, meta-analyses, and methods articles were flagged for hand-searching and cross-referencing against the library of citations identified through electronic database searching. All screening decisions were made and tracked in the DistillerSR database (Evidence Partners, Inc., Manotick, ON, Canada).

Data Extraction

The investigative team created data abstraction forms and evidence table templates. Based on clinical and methodological expertise, two investigators were assigned to the research questions to abstract data from the eligible articles. One investigator abstracted the data, and the second overread the article and the accompanying abstraction to check for accuracy and completeness. Disagreements were resolved by consensus or by obtaining a third reviewer's opinion if consensus was not reached between the first two investigators. To aid in both reproducibility and standardization of data collection, investigators received data abstraction instructions directly on each form created specifically for this project with the DistillerSR data synthesis software program (Evidence Partners Inc., Manotick, ON, Canada). Data reported only in graphs were

estimated quantitatively using Engauge Digitizer version 4.1 software (www.digitizer.sourceforge.net).

We designed the data abstraction forms for this project to collect data required to evaluate the specified eligibility criteria for inclusion in this review, as well as demographic and other data needed for determining outcomes (intermediate outcomes, health outcomes, and safety outcomes). Although we recorded time to clinical worsening (TTCW) as an outcome, we did not analyze it separately in lieu of individual outcomes. As a composite outcome, we found TTCW problematic to assess because it (1) is reported only in relatively few recent studies, (2) is defined differently in different studies, and (3) assigns equal importance to different events in the composite (mortality, hospitalization, transplant). The safety outcomes were framed to help identify adverse events, including bleeding, bruising, infection, liver function abnormalities, headache, flushing, epistaxis, dyspepsia, diarrhea, peripheral edema, nausea, nasal congestion, dizziness, syncope, increased international normalized ratio or prothrombin time.

Data necessary for assessing quality and applicability, as described in the *Methods Guide,*[20] were also abstracted. Before they were used, abstraction form templates were pilot tested with a sample of included articles to ensure that all relevant data elements were captured and that there was consistency and reproducibility between abstractors. Forms were revised as necessary before full abstraction of all included articles. Appendix B lists the elements used in the data abstraction forms. Appendix C contains a bibliography of all articles/studies included in this review, organized alphabetically by author.

Quality (Risk-of-Bias) Assessment of Individual Studies

We evaluated the quality of individual studies by using the approach described in the Methods Guide.[20] For studies of diagnostic tests (KQ 1 and KQ 2), we used QUADAS-2,[23] a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. QUADAS-2 describes risk of bias in four key domains: patient selection, index test(s), reference standard, and flow and timing; each domain is rated as high, low, or unclear risk of bias. For studies of pharmacotherapies, we used the Cochrane Risk of Bias tool, which evaluates random sequence generation, allocation concealment, blinding of participant and personnel, blinding of outcome assessment, incompleteness of outcome data, selective outcome reporting, and other bias.

Two raters independently evaluated each study and differences were resolved by consensus; if consensus could not be reached, then the item was rated as unclear, and the rationale for each differing assessment was described. Results were described for individual domains. If the distribution of ratings permits, methodological domains were examined for association with effects in meta-analysis.

To indicate the summary judgment of the quality of the individual studies, we used the summary ratings of good, fair, or poor based on their adherence to well-accepted standard methodologies and adequate reporting (Table 3).

Table 3. Definitions of overall quality ratings

Quality Rating	Description
Good	A study with the least bias; results are considered valid. A good study has a clear description of the population, setting, interventions, and comparison groups; uses a valid approach to allocate patients to alternative treatments; has a low dropout rate; and uses appropriate means to prevent bias, measure outcomes, and analyze and report results.
Fair	A study that is susceptible to some bias but probably not enough to invalidate the results. The study may be missing information, making it difficult to assess limitations and potential problems. As the fair-quality category is broad, studies with this rating vary in their strengths and weaknesses. The results of some fair-quality studies are possibly valid, while others are probably valid.
Poor	A study with significant bias that may invalidate the results. These studies have serious errors in design, analysis, or reporting; have large amounts of missing information; or have discrepancies in reporting. The results of a poor-quality study are at least as likely to reflect flaws in the study design as to indicate true differences between the compared interventions.

Included meta-analyses were appraised according to criteria adapted from the PRISMA Statement.[21] Grading was outcome-specific; thus, a given study may have been graded of different quality for two individual outcomes reported within that study. Study design also was considered when grading quality. RCTs were graded as good, fair, or poor. Observational studies were graded separately, also as good, fair, or poor. Appendix D summarizes our assessment of the quality and applicability for each included study.

Data Synthesis

Quantitative synthesis (i.e., meta-analysis) was done when we found multiple studies of similar design, population, intervention, comparator and outcome that reported sufficient data for analysis. When a meta-analysis was appropriate, we used random-effects models to quantitatively synthesize the available evidence. We use meta-analyses both to quantify and to attempt to explain between-study variation as well as to calculate summary estimates. When a meta-analysis was not appropriate, we described the reasons, presented data in tabular form, and summarized studies either individually or qualitatively.

For sensitivity and specificity data, we used a binomial model to calculate summary estimates of sensitivity and specificity and associated confidence intervals and summary ROC curve using SAS. Sensitivity analyses were conducted using summary receiver operating characteristic meta-analysis using the diagnostic odds ratio with dr-ROC software (Diagnostic Research Design and Reporting; Glenside, PA). For meta-analysis of correlation coefficients and hazard ratios for observational studies, we used a random effects model implemented in SAS (SAS Institute Inc.; Cary, NC). For treatment effects meta-analysis, we used a random effects model meta-analysis implemented in Comprehensive Meta-Analysis Software (Version 2.2.064, Biostat; Englewood, NJ). We tested for heterogeneity using graphical displays and test statistics (Q and I^2 statistics), while recognizing that the ability of statistical methods to detect heterogeneity may be limited, particularly when the number of studies is small. We present summary estimates and confidence intervals in our data synthesis.

Strength of the Body of Evidence

The strength of evidence for each Key Question was assessed using the approach described in the Methods Guide.[24] The evidence was evaluated using the four required domains: risk of bias, consistency, directness, and precision (Table 4).

Table 4. Strength of evidence required domains

Domain	Rating	How Assessed
Risk of bias	Low Medium High	Assessed primarily through study design (RCT versus observational study) and aggregate study quality
Consistency	Consistent Inconsistent Unknown/not applicable	Assessed primarily through whether effect sizes are generally on the same side of "no effect" and the overall range of effect sizes
Directness	Direct Indirect	Assessed by whether the evidence involves direct comparisons or indirect comparisons through use of surrogate outcomes or use of separate bodies of evidence
Precision	Precise Imprecise	Based primarily on the size of the confidence intervals of effect estimates

Additionally, when appropriate, the studies were evaluated for dose-response association, the presence of confounders that would diminish an observed effect, strength of association (magnitude of effect), and publication bias. These domains were considered qualitatively, and a summary rating of high, moderate, or low strength of evidence was assigned after discussion by two reviewers. In some cases, high, moderate, or low ratings were impossible or imprudent to make; for example, when evidence on the outcome was too weak, sparse, or inconsistent to permit any conclusion to be drawn. In these situations, a grade of insufficient was assigned. This four-level rating scale consists of the following definitions:

- **High**—High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
- **Moderate**—Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
- **Low**—Low confidence that the evidence reflects the true effect. Further research is likely to change the confidence in the estimate of effect and is likely to change the estimate.
- **Insufficient**—Evidence either is unavailable or does not permit estimation of an effect.

Diagnostic evaluation studies (KQs 1 and 2) are generally indirect, as the link between the test intervention and outcome is mitigated by prognosis, management, and the effectiveness of treatments. As a rule of thumb, we considered correlation coefficients greater than 0.7 as strong association, 0.40 to 0.69 as moderate, and less than 0.40 as weak. In our summary strength of evidence assessments for KQs 1 and 2, lack of directness was weighed less heavily and risk of bias most heavily. Thus, we allowed high strength of evidence levels despite the lack of directness among these studies.

Applicability

We assessed applicability across our KQs using the PICOTS format as described in the Methods Guide.[20,25] We used these data to evaluate the applicability to clinical practice, paying special attention to study eligibility criteria, demographic features of the enrolled population (such as age, ethnicity, and sex) in comparison with the target population, version or

characteristics of the intervention used in comparison with therapies currently in use (such as specific components of treatments considered to be supportive therapy), and clinical relevance and timing of the outcome measures. We summarized issues of applicability qualitatively. Because applicability issues may differ for different users, we reported across a range of potential applicability issues (Appendix D).

In diagnostic evaluation studies, we were particularly concerned with the prevalence of PAH versus PH in the study populations compared, the spectrum of underlying type of PAH, and the assessment of adverse events associated with testing. In PAH drug trials, we were particularly concerned with assessing the severity of illness; use of run-in periods and attrition before randomization; use of surrogate or combined outcome measures; short study duration; reporting of adverse events, in particular including those related to administration or monitoring of treatment; sample size sufficient to assess minimally important differences from a patient perspective; and use of intention-to-treat-analysis.

Peer Review and Public Commentary

The peer review process is our principal external quality-monitoring device. Nominations for peer reviewers were solicited from several sources, including the TEP and interested Federal agencies. Experts in cardiology, radiology, vascular surgery, general medicine, and nursing, along with individuals representing stakeholder and user communities, were invited to provide comments; AHRQ and an associate editor also provided comments. The draft report was posted on the AHRQ Web site for 4 weeks, from August 31 to September 28, 2012. We have addressed reviewer comments, revising the report as appropriate, and have documented our responses in a disposition of comments report available on the AHRQ Web site. A list of peer reviewers is given in the preface of this report.

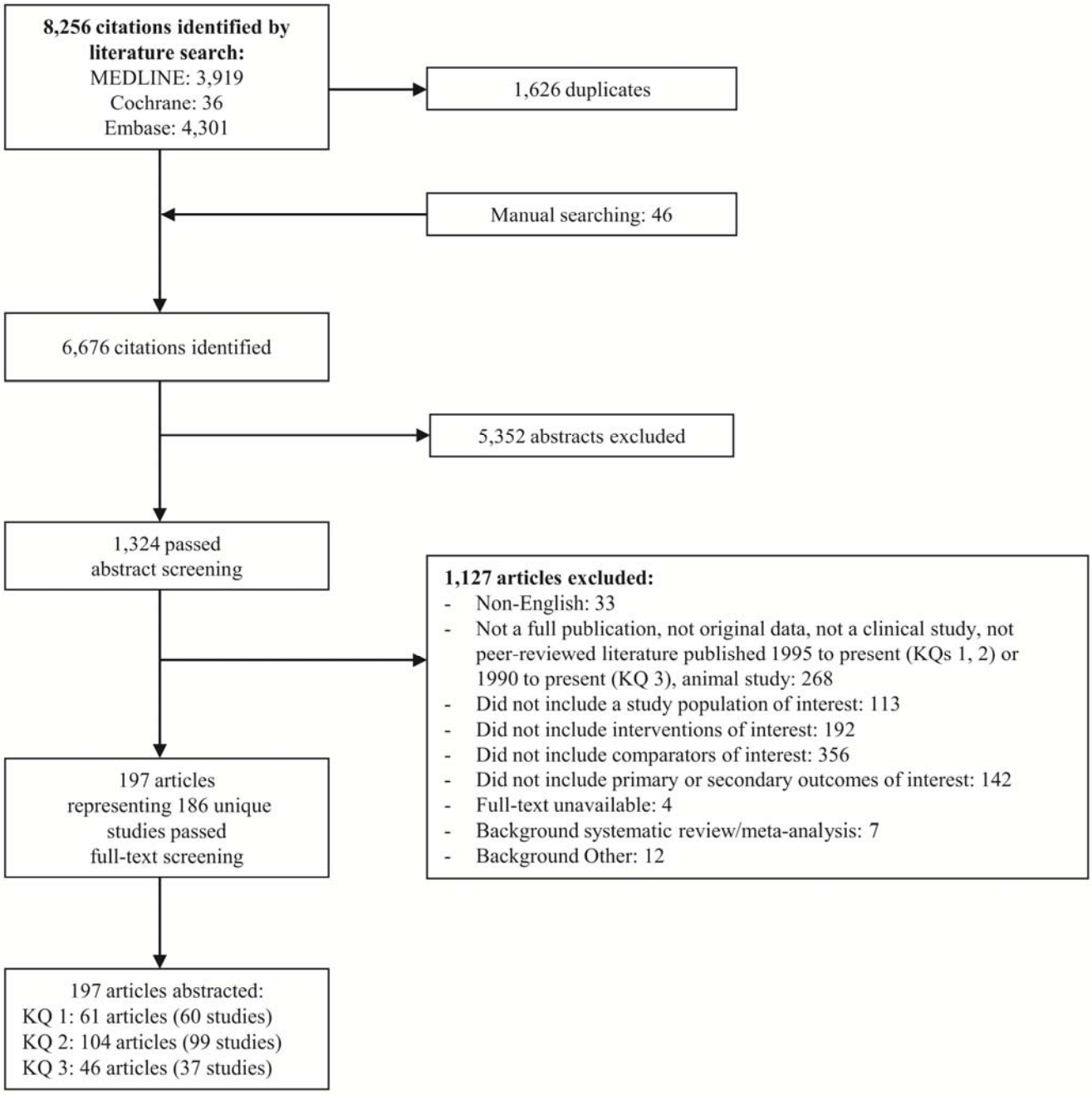
Results

In what follows, we begin by presenting the results of our literature searches. The remainder of the chapter is organized by Key Question (KQ). Under each KQ, we begin by listing the key points of the findings, followed by a brief description of included studies and a study characteristics table, followed by a more detailed synthesis of the evidence. We conducted quantitative analyses (i.e., meta-analyses) where possible, as described in the Methods chapter. Results of these analyses are presented graphically in the form of forest plots and in tabular format. A list of abbreviations and acronyms used in this chapter is provided at the end of the report.

Results of Literature Searches

Figure 3 depicts the flow of articles through the literature search and screening process. Searches of PubMed®, the Cochrane Database of Systematic Reviews, and Embase® yielded 8256 citations, 1626 of which were duplicate citations. Manual searching identified 46 additional citations, for a total of 6676 citations. After applying inclusion/exclusion criteria at the title-and-abstract level, 1324 full-text articles were retrieved and screened. Of these, 1127 were excluded at the full-text screening stage, leaving 197 articles (representing 186 studies) for data abstraction. Appendix C provides a detailed listing of included articles as well as a key to study groupings of primary and companion articles. Appendix E provides a complete list of articles excluded at the full-text screening stage, with reasons for exclusion.

Figure 3. Literature flow diagram



KQ = Key Question
*Article counts by KQ do not add to 197 because some studies were included for multiple KQs.

Description of Included Studies

Overall, we included 186 studies represented by 197 articles: 60 studies were relevant to KQ 1, 99 studies to KQ 2, and 37 studies to KQ 3. Studies were conducted wholly or partly in continental Europe (37%), the United States or Canada (32%), the United Kingdom (7%), Asia (24%), South or Central America (4%), Australia or New Zealand (7%), and other locations (3%). In 11 studies, the location was not reported. Further details on the studies included for each KQ are provided in the relevant results sections below and in Appendix F.

As described in the Methods chapter, we searched ClinicalTrials.gov to identify completed but unpublished studies as a mechanism for ascertaining publication bias. Our search yielded 552 trial records, 257 of which were completed at least 1 year prior to our search of the database and review of the published literature. A single reviewer identified 35 of these records as potentially relevant. We identified and screened publications for 23 of the 35 trial records. Of the 12 trial records for which we did not identify publications, one was considered potentially relevant to KQ 2, and 11 were potentially relevant to KQ 3.

The one study potentially relevant to KQ 2 is an interventional study in patients diagnosed with PAH that was verified as completed with 75 patients in June 2011. It was designed to assess the correlation between plasma brain natriuretic peptide (BNP) and migration inhibitory factor (MIF) levels, both before and after exercise, with 6-minute walk distance (6MWD) and echocardiographic parameters as markers of PAH severity. This study remains unpublished, but if findings are available in the future, the data would add to the BNP correlations with 6MWD and echocardiographic parameters reported here. Although MIF was not in the list of commonly studied biomarkers that we focused on in this report, our findings support the need for additional research into alternative biomarkers that may more effectively assess disease severity.

Of the 11 studies potentially relevant to KQ 3, one was terminated when the drug sitaxsentan was withdrawn from the market, and another study focused on oral treprostinil, which was recently rejected by the FDA. Two more studies were terminated due to slow enrollment, and we could not find any published results. Of the seven remaining studies, four have data uploaded to ClinicalTrials.gov but have yet to be published in the peer-reviewed literature. These studies consist of a dose response study of oral sildenafil that was terminated, the EPITOME-1 and EPITOME-1 Extension studies comparing two types of injectable epoprostenol, and the ATHENA-1 study investigating the addition of ambrisentan to phosphodiesterase-5 (PDE5) inhibitor therapy. These four unpublished trials could potentially provide additional evidence on the comparative safety and effectiveness of pharmacological therapies for PAH in 197 patients. Note that the 37 studies included for KQ 3 involved data for 4192 patients.

The final three studies are either still recruiting, or their true status is unknown. One study, on the effect of treprostinil plus tadalafil versus tadalafil alone, was confirmed as still recruiting in February 2011 and would add to our knowledge of monotherapy versus combination therapy. The final two unpublished studies have not been updated in ClinicalTrials.gov in the last 2 years, and both are studies of novel drug treatments for PAH. One of these studies focuses on the safety and efficacy of fluoxetine, while the other focuses on an endothelin named BQ-123.

Based on our search of ClinicalTrials.gov and the 12 trial records without publications in peer-reviewed literature, we do not believe that there is significant publication bias in the evidence base that would impact our overall findings.

KQ 1: Screening for PAH

KQ 1: For patients with suspected pulmonary arterial hypertension (PAH) and asymptomatic patients at high risk for PAH, what are the comparative effectiveness and safety of echocardiography versus echocardiography plus biomarkers as screening modalities before right heart catheterization to establish the diagnosis of PAH (diagnostic accuracy efficacy)?

Key Points

- For patients suspected of having PAH with elevated systolic pulmonary artery pressure (sPAP) by echocardiography, additional testing with the biomarker N-terminal pro-B-type natriuretic peptide (NT-proBNP) may identify patients who do not have PAH compared with echocardiography sPAP alone (based on one good-quality prospective cohort study) (low strength of evidence).
- For patients suspected of PAH, echocardiographic estimation of right ventricular systolic pressure (RVSP) (or tricuspid gradient [TG]) by tricuspid regurgitation jet velocity (TRV), sPAP by TRV and right atrial pressure (RAP), and pulmonary vascular resistance (PVR) by TRV/velocity-time integral right ventricular outflow tract (VTI_{RVOT}) show reasonably good accuracy compared with right heart catheterization (RHC) (moderate strength of evidence).
- For both asymptomatic patients at high risk for PAH or symptomatic patients suspected of PAH, natriuretic peptide testing (with either BNP or NT-proBNP) shows highly variable sensitivity and specificity estimates (not simultaneously high) for pulmonary hypertension (PH) or PAH diagnosis (low strength of evidence) and moderate correlation with hemodynamic measures by RHC (moderate strength of evidence).
- There were no studies of the safety of biomarker and echocardiography testing, nor were there any studies of combined echocardiographic and biomarker screening of asymptomatic patients at high risk for PAH (insufficient strength of evidence).

Description of Included Studies

We identified 60 unique studies involving a total of 7,096 patients that described the effectiveness of echocardiography or biomarkers in patients with suspected PAH, or in asymptomatic patients at high risk for PAH, as screening modalities before right heart catheterization to establish the diagnosis of PAH.[9,14,26-83] We identified one good-quality study[26] involving 372 patients that compared echocardiography with echocardiography plus biomarkers in patients with suspected PAH, most of whom were symptomatic. There were no other studies directly comparing combinations of echocardiographic and biomarker testing. In order to draw inferences about the comparative effectiveness of other tests, we reviewed the diagnostic accuracy of independent echocardiographic or biomarker testing compared with RHC. By evaluating the relative diagnostic performance of these tests versus a reference standard of RHC, one can impute the comparative effectiveness via indirect comparisons.

Of the 60 included studies, 18 (30%) were rated good quality, 33 (55%) fair quality, and 9 (15%) poor quality. Echocardiographic parameters evaluated were right ventricular (RV) size,

right atrium (RA) size, fractional area change (FAC), tricuspid annular plane systolic excursion (TAPSE), tricuspid lateral annular systolic velocity (S'), right ventricular index of myocardial performance (RIMP), myocardial performance index (MPI), Tei index, systolic pulmonary artery pressure (sPAP), mean pulmonary artery pressure (mPAP), tricuspid regurgitation jet velocity (TRV), velocity-time integral right ventricular outflow tract (VTI_{RVOT}), right ventricular ejection fraction (RVEF), right ventricular systolic pressure (RVSP), and pericardial effusion. Biomarkers evaluated were natriuretic peptides, endothelin-1, uric acid, troponin T, nitric oxide, asymmetric dimethylarginine, cyclic guanosine monophosphate, and D-dimer.

Study Characteristics

Table F-1 in Appendix F summarizes the patient population, study size, test measures, study objectives, and quality rating for each study relevant to KQ 1. Of these studies, 26 were conducted in Europe (including the United Kingdom),[14,26-30,32,35,36,39-41,46,54,55,57,58,60,66,68,70,71,73,76-78] 17 in the United States,[9,33,37,43,45,51-53,56,59,61,65,67,75,80,83] 12 in Asia,[38,47-49,62-64,69,72,79,82] 5 in Australia/New Zealand,[31,42,44,50,81] and 1 in South America.[34] The vast majority of studies included only adults; exceptions were five studies that included only children[45,63,64,74,82] and three studies that included both children and adults.[65,69,79] In studies that reported the sex of participants, a total of 4020 participants were female and 1275 were male. Symptom status of study populations consisted of asymptomatic (3 studies; 481 patients), symptomatic (41 studies; 4394 patients), mixed (8 studies; 1186 patients), and symptoms not described (8 studies; 1035 patients). Of the included studies, 14 compared biomarker levels, 49 evaluated echocardiographic parameters, and 1 assessed echocardiography plus biomarkers as a testing or screening modality in patients with suspected PAH or asymptomatic patients at high risk for developing PAH. BNP and NT-proBNP were the most commonly evaluated biomarkers. The most commonly reported echocardiographic parameters compared with RHC were FAC, mPAP, RIMP, TRV/VTI_{RVOT}, S', sPAP, TRV, and TAPSE.

Detailed Synthesis

Echocardiography Plus Biomarkers for Screening for PAH

We identified only one study (good quality) that gave data on the use of echocardiography and biomarkers in screening patients suspected of having PAH.[26] This study used retrospective data on patients referred for evaluation of precapillary PH to develop a noninvasive diagnostic decision algorithm. This diagnostic algorithm was subsequently tested and validated in a prospective study using data from electrocardiography, serum NT-proBNP, and echocardiography. The goal was to use the aforementioned assessment to distinguish between patients in whom precapillary PH was likely versus those in whom precapillary PH could be excluded with the goal of avoiding unnecessary, invasive RHC procedures. Patients with neither RV strain on ECG (defined as ST-segment deviation and T-wave inversions in leads V1-V3) nor elevated serum NT-proBNP (>80 pg/mL) were considered to have the diagnosis of precapillary PH excluded despite elevated sPAP (≥36 mmHg) by echocardiography.

In 121 patients prospectively evaluated with this algorithm, 44 demonstrated RV strain, which alone had a sensitivity of 66 percent and specificity of 96 percent for identifying patients with precapillary PH. Among the remaining 69 patients, serum NT-proBNP level >80 pg/mL had 100 percent sensitivity and 24 percent specificity. Taken in combination with the decision algorithm, and in patients with echocardiographic estimates of sPAP ≥36 mmHg, the presence of

either RV strain on ECG or serum NT-proBNP >80 pg/mL had a sensitivity of 100 percent and specificity of 19 percent for diagnosis of PAH based on RHC reference standard. By using this decision algorithm to exclude precapillary PH, the investigators concluded that 9 percent of referred patients with elevated sPAP by echocardiography (≥36 mmHg) could avoid undergoing invasive RHC. Excluding patients with RV strain on ECG, serum NT-proBNP testing would have avoided RHC in 16 percent of patients.

Biomarkers for Screening for PAH

Fourteen studies (4 good quality, 7 fair, and 3 poor) evaluated biomarkers in patients with and without PAH.[14,26-28,35,43,58,63,64,68,71,73,79,81] Most studies were of natriuretic peptide (serum NT-proBNP or BNP); we found one study each for urinary cGMP,[28] asymmetric dimethylarginine (ADMA)[79] and plasma endothelin-1 (ET-1).[64] Two studies evaluated biomarkers at baseline for an association with incident diagnosis of PAH,[27,35] while the remaining studies evaluated concurrent biomarker and reference data.[14,26,43,58,63,68,71,73,79,81] Five of these studies were case-control design.[58,68,73,79,81] Four studies permitted calculation of sensitivity and specificity (of a NT-proBNP diagnostic threshold) for diagnosis of PAH (Table 5).[26,58,68,81] One study permitted calculation of sensitivity and specificity of ADMA for diagnosis of PAH.[79] The remaining studies were divided between those reporting biomarker group mean (or median) and standard deviation (or interquartile range) for groups with or without PAH (Table 6) and those reporting the correlation between biomarker level and hemodynamic measures from RHC in the form of a correlation coefficient (n=3)[14,43,63] (Table 7).

Table 5. Diagnostic accuracy of biomarkers for PAH

Study Population (N) Quality	Biomarker	Test Threshold	Reference Diagnostic Criterion	TP	FN	FP	TN	Sensitivity (95% CI)	Specificity (95% CI)	Prevalence
Allanore, 2008[27] SSc patients with echocardiography sPAP<40 mmHg and no NYHA III/IV symptoms (N=101) Good	NT-proBNP	>97th percentile for age/sex	mPAP ≥25 mmHg	6	3	16	77	67 (35 to 88)	83 (74 to 89)	8.8%
Bonderman, 2011[26] Referred for evaluation of suspected PAH; more than half had NYHA III/IV symptoms (N=372) Good	NT-proBNP	>80pg/mL	mPAP >25 mmHg, PCWP <15 mmHg	23	0	35	11	100 (88 to 100)	24 (13 to 39)	33%
Frea, 2011[35] SSc patients with no signs or symptoms of PAH (N=76) Fair	NT-proBNP	>97th percentile for age/sex	mPAP ≥25 mmHg	1	3	6	28	25 (4.6 to 70)	82 (67 to 92)	10.5%
Simeoni, 2008[58] Known SSc-associated PAH and controls with SSc but no PAH (N=20) Poor	NT-proBNP	≥125 pg/mL	mPAP	9	1	3	7	90 (55 to 100)	70 (35 to 93)	50%
Thakkar, 2012[81] SSc patients with PAH, at high risk for PAH, with ILD, or SSc controls without PAH (N=94) Fair	NT-proBNP	≥209.8 pg/mL	mPAP ≥25 mmHg, PCWP ≤15 mmHg	14 13	1 2	0 0	30 19	93 (81 to 100) 87 (70 to 100)	100 (90 to 100) 100 (84 to 100)	33% (PAH vs. SSc controls) 44% (PAH vs. ILD)

Table 5. Diagnostic accuracy of biomarkers for PAH (continued)

Study Population (N) Quality	Biomarker	Test Threshold	Reference Diagnostic Criterion	TP	FN	FP	TN	Sensitivity (95% CI)	Specificity (95% CI)	Prevalence
Williams, 2006[68] SSc patients with PAH and controls with SSc but without PAH (N=109) Fair	NT-proBNP	>91 pg/mL	mPAP >25mmHg at rest or >30mmHg with exercise, PCWP <15 mmHg	38	30	2	39	56 (43 to 68)	95 (83 to 99)	62%
Sanli, 2012[79] Children with unrepaired CHD with or without PAH and healthy controls (N=70) Fair	ADMA	>17 µmol/L	mPAP ≥25 mmHg, PCWP ≤15 mmHg	21	9	10	10	70 (54 to 86)	50 (28 to 72)	60%

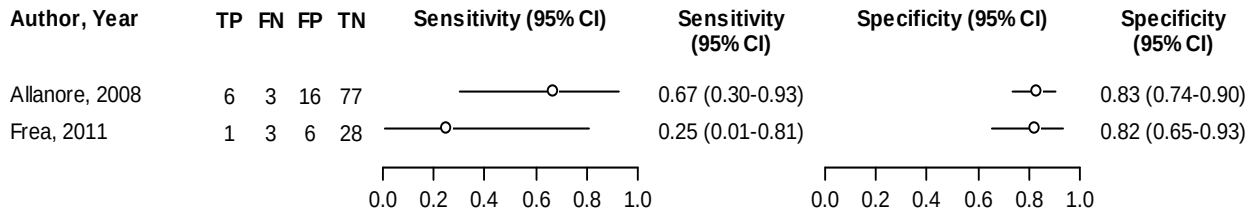
ADMA = asymmetric dimethylarginine; CHD = congenital heart disease; FN = false negative; FP = false positive; ILD = interstitial lung disease; mmHg = millimeter of mercury; mPAP = mean pulmonary artery pressure; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; PAH = pulmonary arterial hypertension; PCWP = pulmonary capillary wedge pressure; SSc = systemic sclerosis; sPAP = systolic pulmonary artery pressure; TN = true negative; TP = true positive

Predicting Incidence of PAH

Two studies of patients with systemic sclerosis reported NT-proBNP levels measured at baseline among patients subsequently diagnosed with PAH.[27,35] At baseline, patients were either without any signs or symptoms suggesting PAH[35] or with no NYHA class III or IV symptoms and echocardiographic estimate of sPAP less than 40 mmHg.[27] In both studies, patients were followed over time for development of symptoms or echocardiographic evidence of elevated sPAP. In followup ranging between 12 mo[35] and 36 mo,[27] approximately 10 percent of patients developed PAH in each study (Table 6).

Mean NT-proBNP levels at baseline were significantly higher among patients subsequently diagnosed with PAH in one study,[27] but not significantly so in the other.[35] This may be related to smaller numbers of patients with PAH or use of a lower mPAP threshold for diagnosis of PAH (25mmHg rather than 35mmHg). Applying a diagnostic threshold based on the 97th percentile by sex and age group in healthy subjects, these two studies found nearly identical specificity, around 83 percent, but sensitivity estimates that are lower with wide confidence limits (Figure 4).

Figure 4. Sensitivity and specificity of NT-proBNP levels for predicting development of PAH

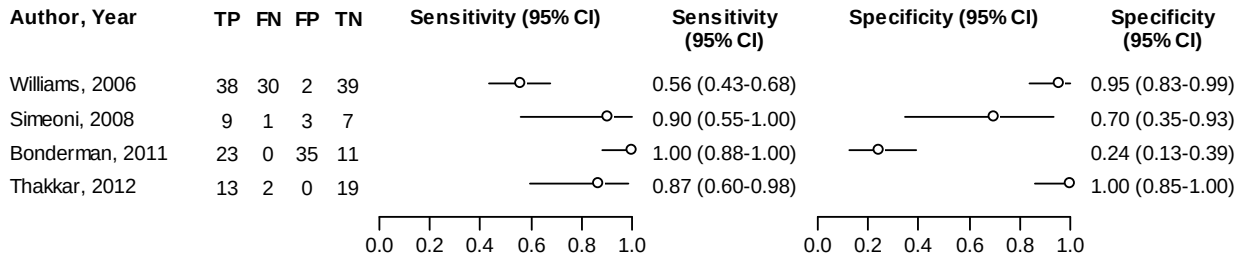


CI = confidence interval; FN = false negative; FP = false positive; TN = true negative; TP = true positive

Diagnosis of Prevalent PAH

Four studies evaluated NT-proBNP for diagnosing PAH; three studies used a case-control design among patients with systemic sclerosis, comparing cases with known PAH to controls with systemic sclerosis but no PAH (Figure 5).[58,68,81] The fourth study included patients referred for evaluation of suspected PAH, but without a specific high-risk diagnosis.[26] Thresholds for NT-proBNP ranged from 80 to 360 pg/mL; except for one study,[81] thresholds were set relatively low compared with the normal ranges. Estimates of the sensitivity and specificity are quite different among these three studies. Differences between sensitivity and specificity estimates among these studies likely stem from both the inclusion criteria and the designs of the study by Bonderman et al.,[26] in which patients were included only if they had elevated sPAP (>36 mmHg) by echocardiography, leading to a population with a high proportion of patients who had elevated NT-proBNP levels. Furthermore, all patients were first screened for evidence of RVH on ECG, before results of NT-proBNP testing were assessed.

Figure 5. Sensitivity and specificity of NT-proBNP for diagnosis of PAH



CI = confidence interval; FN = false negative; FP = false positive; TN = true negative; TP = true positive

Eight studies reported biomarker levels by PAH diagnosis.[14,26,58,68,71,73,79,81] Five studies included patients with systemic sclerosis,[14,58,68,71,81] one included children with congenital heart disease,[79] one included HIV-positive patients,[73] and one (previously described) included patients referred for suspicion of PAH without a specific high-risk diagnosis.[26] Although serum BNP and NT-proBNP levels were consistently more elevated in patients with PAH than those without PAH in these studies, this was represented by a wide range of mean values between studies (Table 6). Three studies reported on a single biomarker each.[28,64,79] ADMA levels were higher among children with PAH and unrepaired congenital heart disease (CHD) than among healthy controls ($p<0.0001$) but not statistically different between those with PAH and unrepaired CHD versus controls with unrepaired CHD but no PAH ($p>0.05$).[79] Urinary cGMP levels were significantly higher among patient with PPH than controls with acute asthma ($p<0.001$) or healthy controls ($p<0.001$).[28] Among children with congenital heart disease with left-to-right shunt, the ratio of pulmonary venous to systemic venous plasma endothelin-1 level distinguished those with PH from those without ($p<0.01$).[64]

Table 6. Biomarker levels by diagnostic group

Study Population (N) Quality	Biomarker	Reference Diagnostic Criterion for PAH	Patients With PAH		Patients Without PAH		Summary Measure
			N	Mean (SD) (pg/mL)	N	Mean (SD) (pg/mL)	Criteria for Verification by RHC
Allanore, 2008[27a] SSc patients with echocardiography sPAP <40 mmHg and no NYHA III/IV symptoms (N=101) Good	NT-proBNP	mPAP ≥25 mmHg, PCWP ≤15 mmHg	8	413 (304)	93	127 (135)	sPAP >40 mmHg, DLCO <50% predicted without pulmonary fibrosis or unexplained dyspnea, negative CT, D-dimer
Bonderman, 2011[26] Referred for evaluation of suspected PAH; more than half had NYHA III/IV symptoms (N=372) Good	NT-proBNP	mPAP >25 mmHg, PCWP <15 mmHg	64	3648 (6541)	57	1489 (3518)	sPAP ≥36 mmHg
Cavagna, 2010[14] SSc patients; symptoms not described (N=135) Good	NT-proBNP	mPAP >25 mmHg, PCWP <15 mmHg	20	189 (44 to 665)[a]	115	84 (39 to 181)[b]	sPAP ≥36 mmHg
Frea, 2011[35a] SSc patients with no signs or symptoms of PAH (N=76) Fair	NT-proBNP	mPAP ≥25 mmHg, PCWP ≤15 mmHg	4	211 (134)	34	127 (100)	TRV ≥3 m/s or sPAP ≥40 mmHg
Ghio, 2004[73] HIV and confirmed PAH; controls with HIV and no known cardiac or pulmonary disease (N=93) Fair	NT-proBNP	NR	16	1412 (574 to 2326)[a]	77	29 (7 to 48)[b]	NR (case-control design)

Table 6. Biomarker levels by diagnostic group (continued)

Study Population (N) Quality	Biomarker	Reference Diagnostic Criterion for PAH	Patients With PAH		Patients Without PAH		Summary Measure
			N	Mean (SD) (pg/mL)	N	Mean (SD) (pg/mL)	Criteria for Verification by RHC
Simeoni, 2008[58] Known SSc-associated PAH and controls with SSc but no PAH (N=20) Poor	NT-proBNP	NR	10	198	10	103	NR (case-control design)
Thakkar, 2012[81] SSc patients with PAH, at high risk for PAH, with ILD, or SSc controls without PAH (N=94) Fair	NT-proBNP	mPAP ≥25 mmHg, PCWP ≤15 mmHg	15	1818 (2367)	19 (ILD) 30 (SSc) 30 (risk)	133 (87) 72 (38) 278 (243)	Echo sPAP ≥40 mmHg or DLCO ≤50% predicted with FVC >85%, DLCO ≥20% or unexplained dyspnea
Williams, 2006[68] SSc patients with PAH and controls with SSc but without PAH (N=109) Fair	NT-proBNP	NR, but PCWP ≤15 mmHg required	68	1474 (2642)	41	139 (150)	NA (case-control design; all patients had RHC)
Cavagna, 2010[14] SSc patients; symptoms not described (N=135) Good	BNP	mPAP ≥25 mmHg, PCWP <15 mmHg	20	74.5 (29 to 196)[a]	115	30 (18 to 49)[b]	sPAP ≥36 mmHg, DLCO <50%pred, 20% decrease DLCO in 1 yr in absence of pulmonary fibrosis, or unexplained dyspnea, negative CT
Gialafos, 2008[71] SSc patients; some symptomatic (N=106) Fair	BNP	NR	37	163 (159)	69	33 (23)	sPAP >40 mmHg (18/37 patients verified by RHC)

Table 6. Biomarker levels by diagnostic group (continued)

Study Population (N) Quality	Biomarker	Reference Diagnostic Criterion for PAH	Patients With PAH		Patients Without PAH		Summary Measure
			N	Mean (SD) (pg/mL)	N	Mean (SD) (pg/mL)	Criteria for Verification by RHC
Sanli, 2012[79] Children with unrepaired CHD with or without PAH and healthy controls (N=70) Fair	ADMA	mPAP≥25 mmHg, PCWP ≤ 15 mmHg	30	23.1 (9.2)	20 20	19.6 (7.4) (CHD controls) 17.1 (5.6) (healthy controls)	All patients verified by RHC
Bogdan, 1998[28] PAH patients (N=19) and controls (N=30) Poor	Urinary cGMP	NR	19	251 (26) nmol/mmol creatinine	30 7	51 (4) healthy controls 71 (8) asthmatic controls	NR (case-control design)
Tutar 1999[64] Children with left-to-right shunt (N=23) and healthy controls (N=11) Fair	Plasma endothelin-1 (ratio of pulmonary venous and systemic venous level)	Ratio of simultaneous mPAP to aortic mean pressure > 0.5	9	1.10 (0.35)	14	0.90 (0.16)	NR (case-control design)

ADMA = asymmetric dimethylarginine; CHD = congenital heart disease; CT = computed tomography; DLCO = diffusion capacity of the lung for carbon monoxide; FVC = forced vital capacity; ILD = interstitial lung disease; mmHg = millimeter of mercury; mPAP = mean pulmonary artery pressure; m/s = meters per second; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; PAH = pulmonary arterial hypertension; PCWP = pulmonary capillary wedge pressure; RHC = right heart catheterization; SD = standard deviation; sPAP = systolic pulmonary artery pressure; RHC = right heart catheterization; yr = year/years

[a]Studies that assessed baseline NT-proBNP as predictors of future development of PAH.

[b]Median interquartile range.

Four studies examined the correlation between either serum BNP or NT-proBNP levels and hemodynamic parameters measured at RHC. Statistically significant correlations were found between the biomarker level and CO, mPAP, PVR, mean right atrial pressure (mRAP), and sPAP; these correlations were of moderate strength for all parameters (Table 7). One study of ADMA found no correlation between ADMA levels and mPAP, sPAP, or PVR.[79] One study each of urinary cGMP[28] and plasma endothelin-1[64] reported isolated positive correlations among many negative correlations for which incomplete data were reported.

Table 7. Correlations of biomarkers with RHC in PAH

Study Population (N) Quality	Biomarker	RHC Parameter	Total N	Correlation (p-value)
Machado, 2006[43] Sickle cell disease (N=416) Poor	NT-proBNP	CO	37	-0.43 (0.006)
	NT-proBNP	mPAP	37	0.43 (0.006)
	NT-proBNP	PVR (NR)	37	0.51 (0.001)
	NT-proBNP	sPAP	37	0.59 (0.002)
Thakkar, 2012[81] SSc patients with PAH, at high risk for PAH, with ILD or SSc controls without PAH (N=94) Fair	NT-proBNP	mPAP	15	0.63 (0.013)
	NT-proBNP	mRAP	15	0.77 (0.006)
	NT-proBNP	PVR	15	0.76 (0.005)
	NT-proBNP	sPAP	94	0.65 (<0.0001)
Cavagna, 2010[14] SSc patients; symptoms not described (N=135) Good	NT-proBNP	mPAP	115	0.61 (0.001)
	BNP	mPAP	135	0.72 (0.002)
Toyono, 2008[63] Children with VSD and severe PH (N=24) Good	BNP	PVR (Fick)	24	0.56 (0.004)
Sanli, 2012[79] Children with unrepaired CHD with or without PAH and healthy controls (N=70) Fair	ADMA	mPAP	30	-0.10 (>0.05)
	ADMA	sPAP	30	-0.02 (>0.05)
	ADMA	PVR	30	-0.19 (>0.05)
Bogdan, 1998[28] PAH patients (N=19) and controls (N=30) Poor	Urinary cGMP	Cardiac Index	19	-0.65 (0.003)
Tutar 1999[64] Children with left-to-right shunt (N=23) and healthy controls (N=11) Fair	Plasma endothelin-1 level (ratio of pulmonary to systemic venous)	mPAP	23	0.57 (<0.005)

ADMA = asymmetric dimethylarginine; BNP = B-type natriuretic peptide; CO = cardiac output; mPAP = mean pulmonary artery pressure; mRAP = mean right atrial pressure; NR = not reported; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PAH = pulmonary arterial hypertension; sPAP = systolic pulmonary artery pressure; PVR = pulmonary vascular resistance; RHC = right heart catheterization

Echocardiography for Diagnosing PAH

Twenty-six studies assessed echocardiography in evaluating patients suspected of PAH. All studies reported data that compared a single hemodynamic parameter at a time. Nineteen studies (6 good quality, 10 fair, 3 poor) reported the diagnostic accuracy of echocardiographic estimates of pulmonary pressures based on TRV measurement, with or without estimate of RAP, compared with a reference standard diagnosis based on RHC (Table 8).[29,30,32,34,36-40,42,46,50,51,59,60,75,77,78,83]

Six studies used a variable estimate of RAP (based on inferior vena cava size and inspiratory variation or jugular venous pressure) to calculate sPAP;[29,32,38,40,51,83] five studies calculated sPAP using a fixed value for RAP;[37,50,59,60,78] and eight studies used TG or TRV.[30,34,36,39,42,46,75,77]

Eleven of these studies were of patients with systemic sclerosis (or other collagen vascular disease) with suspected PAH based on symptoms.[30,32,36,37,39,40,46,50,59,77,78] Four studies evaluated liver transplant candidates;[29,38,51,60] two studies included patients with sickle cell disease;[34,75] and two studies had patients referred for evaluation of suspected PAH without a single high-risk condition.[42,83]

Table 8. Diagnostic accuracy of echocardiographic parameters for diagnosis of PAH

Study Population (N) Quality	Test Parameter	Test Threshold	Reference Diagnostic Criterion	TP	FN	FP	TN	Sensitivity (95% CI)	Specificity (95% CI)	Prevalence
Hua, 2008[38] Liver transplant candidates (N=105) Good	sPAP 4 * TRV^2 + RAP	≥30 mmHg	mPAP ≥25 mmHg (PVR ≥240 dyne*sec/cm^5 PCWP <15 mmHg	4	0	18	83	100 (47 to 100)	82 (73 to 89)	4%
Torregrosa, 2001[60] Liver transplant candidates (N=94) Fair	sPAP 4 * TRV^2 + 10 sPAP, PAT	≥40 mmHg sPAP ≥40 mmHg or PAT <100 ms	mPAP ≥25 mmHg or PVR >120 dynes*s/cm^5	4 5	1 0	3 5	35 33	80 (45 to 100) 100 (40 to 100)	92 (84 to 96) 87 (76 to 98)	12%
Phung, 2009[50] SSc patients referred with or without suspicion of PAH; 10% had NYHA III/IV symptoms (N=184) Good	sPAP 4 * TRV^2 + 10	>40 mmHg	mPAP ≥25 mmHg	23	0	18	119	100 (88 to 100)	87 (80 to 92)	14%
Pilatis, 2000[51] Liver transplant candidates (N=55) Fair	sPAP 4 * TRV^2 + RAP	>40 mmHg	mPAP ≥25 mmHg	5	3	1	46	62 (24 to 91)	98 (89 to 100)	14%
Ruiz-Irastorza, 2012[78] SLE patients in cohort study, regardless of symptoms of dyspnea (N=245) Fair	sPAP 4 * TRV^2 + 5	≥40 mmHg ≥30 mmHg ≥40 mmHg *2	mPAP ≥25 mmHg	12 12 12	0 0 0	19 110 5	212 121 226	100 (75 to 100) 100 (75 to 100) 100 (75 to 100)	92 (88 to 95) 52 (46 to 59) 98 (96 to 100)	5% 5% 5%

Table 8. Diagnostic accuracy of echocardiographic parameters for diagnosis of PAH (continued)

Study Population (N) Quality	Test Parameter	Test Threshold	Reference Diagnostic Criterion	TP	FN	FP	TN	Sensitivity (95% CI)	Specificity (95% CI)	Prevalence
Steen, 2008[59] SSc patients with suspected PAH based on symptoms or signs (N=54) Fair	sPAP 4 * TRV^2 + 10	>20 mmHg increase over resting	mPAP >25 mmHg (rest) or >30 mmHg (exercise)	21	5	3	25	81 (61 to 93)	89 (72 to 98)	48%
Colle, 2003[29] Liver transplant candidates (N=165) Good	sPAP 4 * TRV^2 + RAP	≥30 mmHg	mPAP >25 PCWP <15 PVR >120 dynes*s/cm^5	8	2	6	149	80 (44 to 97)	96 (92 to 99)	6%
Hsu, 2008[37] SSc patients with dyspnea or other clinical features suggestive of PAH (N=49) Good	sPAP 4 * TRV^2 + 10	>47 mmHg	sPAP>25 mmHg	14	10	1	24	58 (37 to 78)	96 (80 to 100)	49%
Denton, 1997[32] SSc patients suspected of PAH, most due to reduced DLCO (N=93) Fair	sPAP 4 * TRV^2 + JVP	≥30 mmHg	sPAP ≥30 mmHg "provided PCWP was normal"	19	2	3	9	90 (70 to 99)	75 (43 to 95)	64%
Kovacs, 2010[40] Patients with CVD some with symptoms (N=52) Good	sPAP 4 * TRV^2 + RAP	>40 mmHg	sPAP >40 mmHg with exercise and PCWP ≤20 mmHg	11	5	10	18	69 (41 to 89)	64 (44 to 81)	36%

Table 8. Diagnostic accuracy of echocardiographic parameters for diagnosis of PAH (continued)

Study Population (N) Quality	Test Parameter	Test Threshold	Reference Diagnostic Criterion	TP	FN	FP	TN	Sensitivity (95% CI)	Specificity (95% CI)	Prevalence
Arcasoy, 2003[83] Advanced lung disease, undergoing evaluation for lung transplantation (N=374) Good	sPAP RV finding	≥45 mmHg RVH, dilation or systolic dysfunction	sPAP ≥45 by RHC	51 78	9 17	48 120	58 157	85 (73 to 93) 82 (73 to 89)	55 (45 to 64) 57 (51 to 62)	36% 27%
Mukerjee, 2004[46] SSc patients with suspected PAH, symptoms of exercise limitation and reduced DLCO (N=137) Fair	TG 4 * TRV^2	≥40 mmHg	mPAP>25mmHg or resting PVR>200 dyne*sec/cm^5 mPAP>30mmHg with exercise	57	42	5	33	58 (47 to 67)	87 (72 to 96)	72%
Condliffe, 2011[30] SSc patients with suspected PAH; symptoms not described (N=89) Fair	TRV	≥35 mmHg (≥2.96 m/s)	mPAP ≥ 25 mmHg and PCWP ≤15 mmHg	42	5	10	10	89 (77 to 96)	50 (27 to 73)	70%
Fitzgerald, 2012[75] Adults with SCD (N=75) Poor	TRV	≥ 2.5 m/s	mPAP ≥ 25 mmHg mPAP≥25 mmHg and PCWP ≤15 mmHg	9 3	0 0	16 22	50 50	100 (67 to 100) 100 (0 to 100)	76 (65 to 86) 69 (59 to 80)	12% 4%
Fonseca, 2012[34] Sickle cell disease; symptoms not described (N=80) Fair	TRV	>2.5 m/s	mPAP ≥25 mmHg mPAP ≥25 mmHg and PCWP ≤15 mmHg	8 3	0 0	18 23	48 48	100 (62 to 100) 100 (0 to 100)	73 (62 to 84) 68 (57 to 78)	11% 4%

Table 8. Diagnostic accuracy of echocardiographic parameters for diagnosis of PAH (continued)

Study Population (N) Quality	Test Parameter	Test Threshold	Reference Diagnostic Criterion	TP	FN	FP	TN	Sensitivity (95% CI)	Specificity (95% CI)	Prevalence
Hachulla, 2005[36] SSc patients; some symptomatic (N=599) Poor	TRV	≥3 m/s or ≥2.5 m/s with unexplained dyspnea	mPAP ≥25 mmHg rest or ≥30 mmHg with exercise and PCWP ≤15 mmHg	18	0	15	419	100 (85 to 100)	97 (94 to 98)	4%
Jansa, 2011[39] SSc patients some with dyspnea (N=203) Fair	TRV	>30 mmHg (>2.74 m/s)	mPAP ≥25 mmHg and PCWP ≤15 mmHg	6	0	10	186	100 (61 to 100)	95 (91 to 98)	3%
Low, 2011[42] Referred for evaluation of suspected or definite PAH, most with symptoms (N=200) Poor	TRV	≥36 mmHg (≥3 m/s)	mPAP >25 mmHg PCWP, LAP or LVEDP ≤15 mmHg PVR >3WU	58	0	8	128	100 (95 to 100)	94 (89 to 97)	30%
Rajaram, 2012[77] CTD suspected of PH based on symptoms or screening tests (N=81) Fair	TRV	NR ≥ 30 mmHg (≥2.74 m/s) ≥40 mmHg (≥3.16 m/s) ≥50 mmHg (≥3.54 m/s)	mPAP ≥25 mmHg and PCWP ≤15 mmHg	27 52 47 39	28 3 8 16	4 13 4 1	18 9 18 21	49 (36 to 62) 95 (89 to 100) 86 (76 to 95) 71 (59 to 83)	82 (66 to 98) 41 (20 to 62) 82 (66 to 98) 95 (87 to 100)	71%

Table 8. Diagnostic accuracy of echocardiographic parameters for diagnosis of PAH (continued)

Study Population (N) Quality	Test Parameter	Test Threshold	Reference Diagnostic Criterion	TP	FN	FP	TN	Sensitivity (95% CI)	Specificity (95% CI)	Prevalence
Dahiya, 2010[31] Referred for evaluation of suspected PH; all patients had dyspnea (N=114) Good	TRV/VTI_{RVOT}	>0.16	PVR >2 WU	47	3	2	20	94 (83 to 99)	91 (71 to 99)	69%
Lindqvist, 2011[41] Patients with PH undergoing RHC (N=30) Fair	TRV/VTI_{RVOT}	>0.175	PVR >3 WU	16	2	1	6	88 (65 to 99)	86 (42 to 100)	72%
Rajagopalan, 2009[52] Known pulmonary hypertension (N=52) Fair	TRV/VTI_{RVOT}	>0.16	PVR >2 WU	41	4	0	7	91 (79 to 98)	100 (65 to 100)	87%
Roule, 2010[55] Known PH (N=37) Good	TRV/VTI_{RVOT}	>0.14	PVR >2 WU	28	2	3	4	93 (78 to 99)	57 (18 to 90)	81%
Vlahos, 2007[65] Known or suspected pulmonary hypertension (N=12) Fair	TRV/VTI_{RVOT}	>0.38	PVR >8 WU	6	2	0	4	75 (35 to 97)	100 (47 to 100)	67%

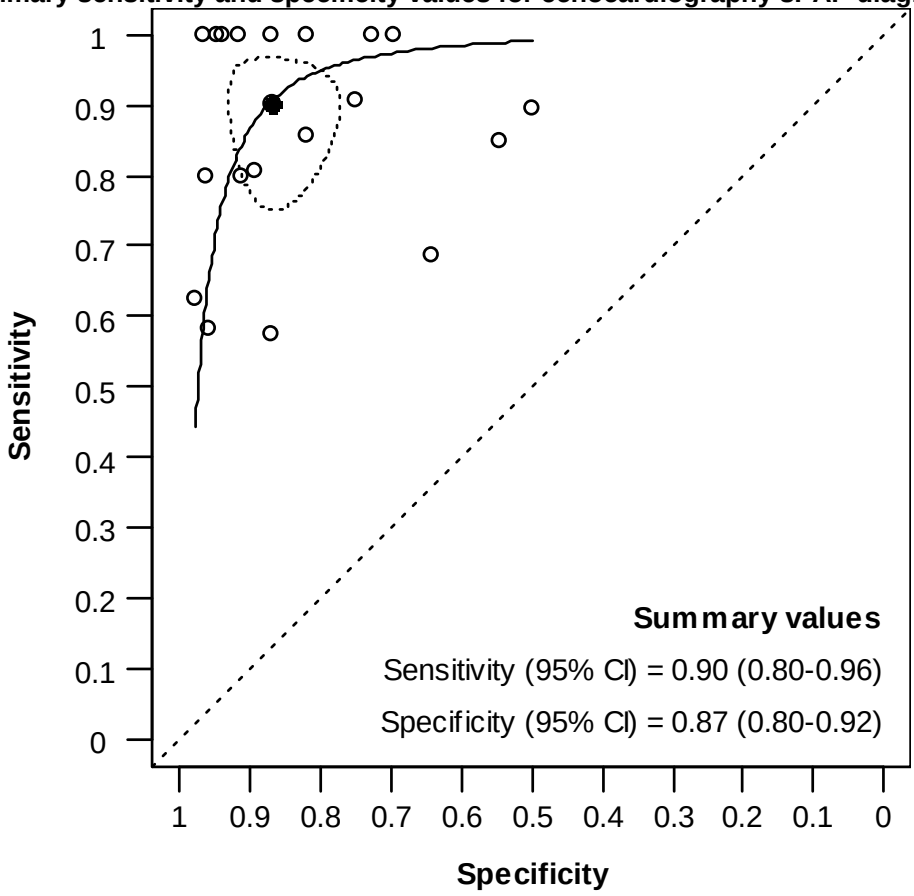
Table 8. Diagnostic accuracy of echocardiographic parameters for diagnosis of PAH (continued)

Study Population (N) Quality	Test Parameter	Test Threshold	Reference Diagnostic Criterion	TP	FN	FP	TN	Sensitivity (95% CI)	Specificity (95% CI)	Prevalence
Ajami, 2011[68,69] Children and young adults with congenital heart disease referred for RHC (N=20) Good	TRV/VTI_{RVOT}	>0.2	PVR >8 WU	9	1	1	9	90 (55 to 100)	90 (55 to 100)	50%
Cevik, 2012[74] Children with CHD and healthy controls (N=70) Fair	RVMPI	NR	mPAP ≥25 mmHg and PCWP ≤15 mmHg	14	16	2	38	47 (29 to 64)	95 (88 to 100)	43%
	S’			21	9	2	38	70 (54 to 86)	95 (88 to 100)	
	$sPAP/VTI_{RVOT}$			17	13	5	35	57 (39 to 74)	88 (77 to 98)	
Rajagopalan, 2009[52] Known pulmonary hypertension (N=52) Fair	S’	< 10 cm/s	sPAP >75 mmHg	10	5	2	15	67 (43 to 90)	88 (73 to 100)	47%

CHD = congenital heart disease; CI = confidence interval; cm/s = centimeters per second; CTD = connective tissue disease; FAC = fractional area change; FN = false negative; FP = false positive; JVP = jugular venous pressure; LVEDP = left ventricular end-diastolic pressure; mmHg = millimeter of mercury; mPAP = mean pulmonary artery pressure; MPI = myocardial performance index; NR = not reported; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PAH = pulmonary arterial hypertension; PAT = pulmonary acceleration time; PCWP = pulmonary capillary wedge pressure; PH = pulmonary hypertension; PPH = primary pulmonary hypertension; PVR = pulmonary vascular resistance; RA = right atrium; RIMP = right index of myocardial performance; RV = right ventricle; RVH = right ventricular hypertrophy; RVMPI = right ventricular myocardial performance index; S’ = tricuspid lateral annular systolic velocity; sPAP = systolic pulmonary artery pressure; SSc = systemic sclerosis; TAPSE = tricuspid annular plane systolic excursion; TG = tricuspid gradient; TN = true negative; TP = true positive; TRV = tricuspid regurgitant jet velocity; VSD = ventricular septal defect; VTI_{RVOT} = velocity-time integral of right ventricular outflow tract; WU = Wood unit

Sensitivity of estimates ranged from 58 to 100 percent, while specificity estimates ranged from 55 to 98 percent. The paired sensitivity and specificity values are shown in Figure 6 in receiver operating curve space. The studies with the greatest degree of verification bias (large proportion of test-negative patients with no RHC verification of disease status) tend to have both high specificity and sensitivity estimates. Four studies of liver transplant candidates were the only ones to have complete RHC verification, and these studies had sensitivity estimates from 62 to 100 percent and specificity estimates from 82 to 98 percent.[29,38,51,60]

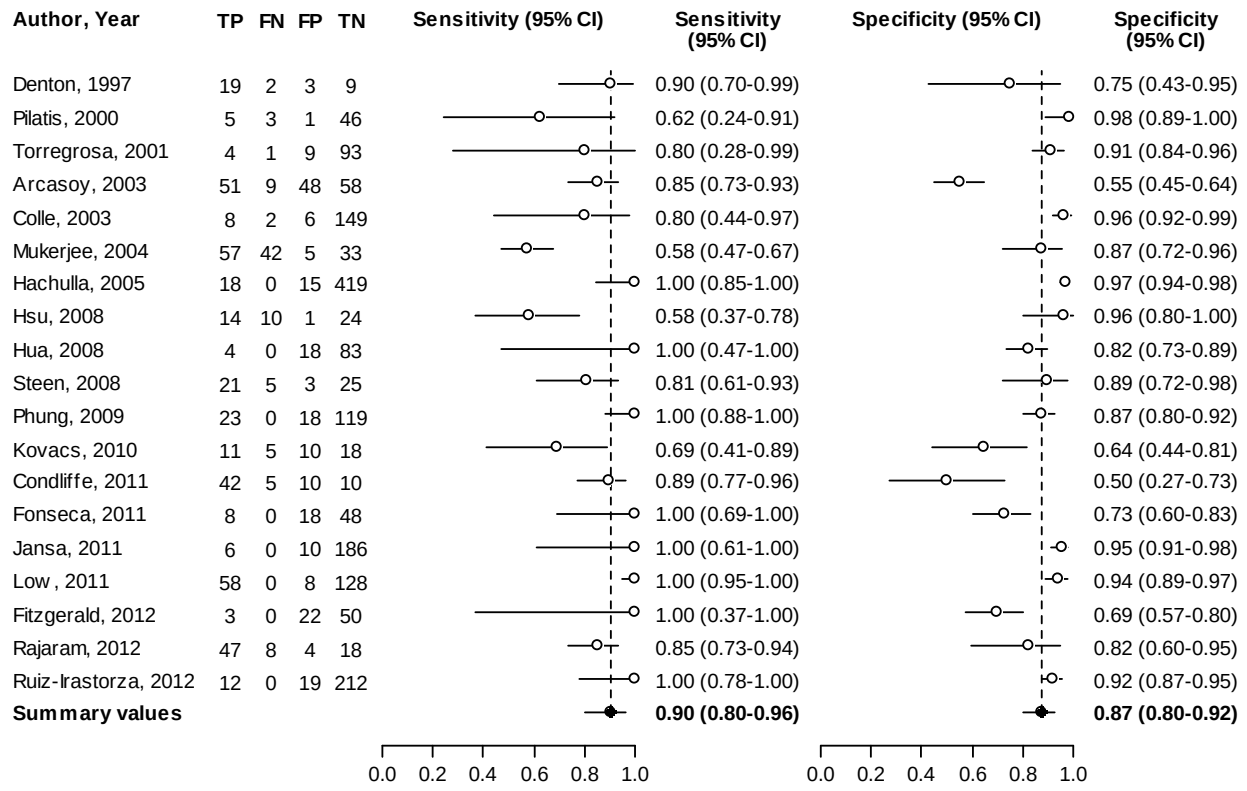
Figure 6. Summary sensitivity and specificity values for echocardiography sPAP diagnosis of PH



CI = confidence interval

Meta-analysis of the 19 studies yielded summary estimates for sensitivity and specificity of 88 percent, with confidence region as shown in Figure 7. There was moderate heterogeneity (I^2=61.9%). In an effort to explain the between-study variation, we undertook a sensitivity analysis based on features we suspected might account for variation and that had suitable distributions among the studies. The results of the sensitivity analyses are shown in Table 9.

Figure 7. Sensitivity and specificity of echocardiography sPAP for diagnosis of PAH



CI = confidence interval; FN = false negative; FP = false positive; TN = true negative; TP = true positive

Table 9. Sensitivity analysis of echocardiography sPAP by study characteristics

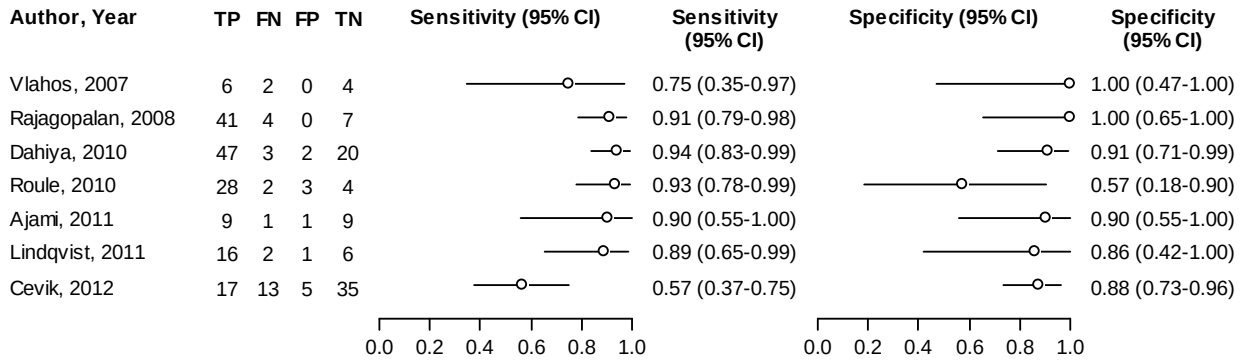
Study Characteristic	Number of Studies (Patients)	Summary Sensitivity (95% CI)	Summary Specificity (95% CI)	I^2
Prevalence				
Less than 15%	10 (1638)	90.6 (84.9 to 94.2)	90.8 (85.2 to 94.4)	0
15% or more	9 (821)	83.7 (71.8 to 91.2)	83.6 (71.7 to 91.1)	62.7%
Diagnosis				
Liver transplant	4 (432)	79.7 (72.5 to 85.4)	93.8 (91.1 to 95.8)	0
Systemic sclerosis	10 (1474)	88.7 (82.2 to 93.1)	89.7 (83.6 to 93.7)	52.5%
Other (SSD, CVD)	5 (553)	90.3 (71.8 to 97.2)	73.2 (42.7 to 90.9)	73.6%
RAP Method				
None or fixed	13 (1891)	89.9 (84.5 to 93.6)	88.9 (83.1 to 92.9)	56.1%
Variable	6 (561)	81.4 (70.1 to 89.1)	85.0 (75.3 to 91.4)	63.8%

CI = confidence interval; CVD = collagen vascular disease; RAP = right atrial pressure; sPAP = systolic pulmonary artery pressure; SSD = sickle cell disease

Studies with lower prevalence of PH (less than 15% of study subjects) showed greater homogeneity than studies with higher prevalence of PH. These 10 low-prevalence studies included the four studies of liver transplant patients (which had complete verification of test-negative subjects) and 6 studies that had high degree of verification bias. The studies among liver transplant patients had no important heterogeneity compared with 10 studies of systemic sclerosis patients or studies in patients with other diagnoses. The method of correction for RAP (fixed or none versus variable estimate) did not explain between-study heterogeneity.

Seven studies (three good quality, three fair, 1 poor) evaluated the echocardiographic estimation of PVR using TRV/VTI_{RVOT} against RHC diagnosis of elevated PVR (Figure 8).[31,41,52,55,65,69,74] Three of these studies included patients with known PH.[41,52,55] Two studies used a threshold for PVR much higher than that used for diagnosis (8 Wood units versus 2 Wood units)[65,69] with the goal of distinguishing more severe PAH; these studies also used a higher test threshold of 0.2 and 0.38 compared with 0.14 to 0.175. Sensitivity ranged from 57 to 94 percent, while specificity ranged from 57 to 100 percent.

Figure 8. Sensitivity and specificity of TRV/VTI_{RVOT} for diagnosis of PAH



CI = confidence interval; FN = false negative; FP = false positive; TN = true negative; TP = true positive

Echocardiographic Parameters by Diagnostic Group

Fifteen studies reported data on the mean (or median) and standard deviation (or interquartile range) for specific echocardiographic parameters for patients with and without PAH (Table 10). Two of these studies reported echocardiographic values at baseline for prospectively identified incident cases of PAH.[27,35] In one study, the diagnostic categories distinguished between primary PAH and chronic thromboembolic pulmonary hypertension.[48]

Table 10. Echocardiographic parameter values by diagnostic group

Study Population (N) Quality	Echocardio-graphic Parameter	Criteria for Verification by RHC	Reference Diagnostic Criterion	Patients With PAH		Patients Without PAH		P-value
				N	Mean (SD)	N	Mean (SD)	
Ruan, 2007[56] Known PAH and healthy controls (N=180) Fair	FAC	NR (case-control design)	NR	70	19 (10)	35	53 (10)	NR
Fukuda, 2011[72] Patients with known PH (N=67) Fair	FAC	NR (case-control design)	mPAP > 25 mmHg	45	37 (13)	22	51 (1)	<0.001
Rajagopalan, 2009[52] Known pulmonary hypertension (N=52) Fair	FAC	NR (case-control design)		32	31 (12)	15	52 (5)	<0.05
Bonderman, 2011[26] Referred for evaluation of suspected PAH; more than half had NYHA III/IV symptoms (N=372) Good	RA size	sPAP ≥36 mmHg	mPAP >25 mmHg, PCWP <15 mmHg	64	58.7 (10.9)	57	59.1 (11.5)	0.87
Hachulla, 2005[36] SSc patients; some symptomatic (N=599) Poor	RA size (transverse) RA size (longitudinal)	NR (case-control design)	mPAP ≥25 mmHg rest or ≥30 mmHg with exercise and PCWP ≤15 mmHg	18	38.7 (8.3) 48.3 (7.2)	548	34.3 (7.0) 42.1 (7.2)	0.01 0.0001
Fukuda, 2011[72] Patients with known PH (N=67) Fair	RIMP	NR (case-control design)	mPAP >25 mmHg	45	0.4 (0.1)	22	0.2 (0.1)	<0.001

Table 10. Echocardiographic parameter values by diagnostic group (continued)

Study Population (N) Quality	Echocardio-graphic Parameter	Criteria for Verification by RHC	Reference Diagnostic Criterion	Patients With PAH		Patients Without PAH		P-value
				N	Mean (SD)	N	Mean (SD)	
Tei, 1996[61] Known PPH and health controls (N=53) Poor	RIMP	NR (case-control design)	NR	26	0.89 (0.25)	37	0.28 (0.04)	<0.001
Gialafos, 2008[71] SSc patients. Some were symptomatic (N=106) Fair	RIMP	sPAP >40 mmHg (18/37 patients verified by RHC)	NR	37	0.41 (0.03)	69	0.37 (0.02)	<0.001
Bonderman, 2011[26] Referred for evaluation of suspected PAH; more than half had NYHA III/IV symptoms (N=372) Good	RV size	sPAP ≥36 mmHg	mPAP >25 mmHg, PCWP <15 mmHg	64	44 (9.2)	57	38.2 (6.9)	<0.001
Hachulla, 2005[36] SSc patients; some symptomatic (N=599) Poor	RV size	NR (case-control design)	mPAP ≥25 mmHg rest or ≥30 mmHg with exercise and PCWP ≤15 mmHg	18	33.0 (5.9)	548	30.0 (6.6)	0.061
Rajagopalan, 2009[52] Known pulmonary hypertension (N=52) Fair	RV size (end-diastolic area) RV size (end systolic area)	NR (case-control design)		32	27 (11) 19 (9)	15	20 (4) 9 (3)	<0.05 <0.05
Ruan, 2007[56] Known PAH and healthy controls (N=180) Fair	RV size	NR (case-control design)	NR	70	28 (9)	35	14 (6)	NR

Table 10. Echocardiographic parameter values by diagnostic group (continued)

Study Population (N) Quality	Echocardio-graphic Parameter	Criteria for Verification by RHC	Reference Diagnostic Criterion	Patients With PAH		Patients Without PAH		P-value
				N	Mean (SD)	N	Mean (SD)	
Fukuda, 2011[72] Patients with known PH (N=67) Fair	S'	NR (case-control design)	mPAP >25 mmHg	45	11.8 (2.9)	22	14.1 (2.4)	<0.001
Rajagopalan, 2009[52] Known pulmonary hypertension (N=52) Fair	S'	NR	NR	32	10.9 (2.9)	15	13.8 (2.8)	<0.01
Ruan, 2007[56] Known PAH and healthy controls (N=180) Fair	S'	NR (case-control design)	NR	70	8 (3)	35	15.8 (5.5)	<0.05
Bonderman, 2011[26] Referred for evaluation of suspected PAH; more than half had NYHA III/IV symptoms (N=372) Good	sPAP	sPAP ≥36 mmHg	mPAP >25 mmHg PCWP <15 mmHg	64	82.6 (24.3)	57	55.2 (16.3)	<0.001
Ruan, 2007[56] Known PAH and healthy controls (N=180) Fair	sPAP	NR (case-control design)	NR	70	73 (6)	35	21 (6)	NR
Torregrosa, 2001[60] Liver transplant candidates (N=94) Fair	sPAP	NA (all patients had RHC)	mPAP ≥25 mmHg PVR >120 dyne*sec/cm^5	5	54 (15)	102	36 (5)	<0.001

Table 10. Echocardiographic parameter values by diagnostic group (continued)

Study Population (N) Quality	Echocardio-graphic Parameter	Criteria for Verification by RHC	Reference Diagnostic Criterion	Patients With PAH		Patients Without PAH		P-value
				N	Mean (SD)	N	Mean (SD)	
Fukuda, 2011[72] Patients with known PH (N=67) Fair	sPAP	NR (case-control design)	mPAP >25 mmHg	45	67 (23)	22	20 (10)	0.0001
Fitzgerald, 2012[75] Adults with SCD (N=75) Poor	TRV	TRV ≥2.5	mPAP ≥25 mmHg, PCWP ≤15 mmHg	9	2.7 (0.16)	16	3.1 (0.68)	0.12
Hammerstingl, 2012[76] Patients with PH undergoing RHC (N=155) Fair	sPAP RVDs RVDd	sPAP >30 mmHg, all patients had RHC	mPAP ≥25 mmHg, PCWP ≤15 mmHg	36 36 36	58.3 (23.6) 2.4 (1.2) 3.4 (1.6)	119 119 119	49.9 (14.2) 2.4 (1.1) 3.3 (1.3)	0.009 0.8 0.88
Fukuda, 2011[72] Patients with known PH (N=67) Fair	TAPSE	NR (case-control design)	mPAP >25 mmHg	45	18 (4)	22	21 (3)	<0.001
Cevik, 2012[74] Children with CHD and healthy controls (N=70) Fair	RVMPI/RIMP S' (Ts') TAPSE $sPAP/VTI_{RVOT}$ $sPAP/VTI_{RVOT}$	NA (all patients had CHD)	mPAP ≥25 mmHg, PCWP ≤15 mmHg	30	0.45 (0.14) 0.13 (0.09-0.58) 1.96 (1.03-3.22) 1.3 (0.0-8.8) 1.0 (0.0-9.0)	40	0.35 (0.08) 0.13 (0.10-0.18) 2.53 (1.1-4.25) 0.5 (0.0-1.2) 0.6 (0.01-1.0)	<0.001 0.42 0.10 <0.001 0.015

Table 10. Echocardiographic parameter values by diagnostic group (continued)

Study Population (N) Quality	Echocardio-graphic Parameter	Criteria for Verification by RHC	Reference Diagnostic Criterion	Patients With PAH		Patients Without PAH		P-value
				N	Mean (SD)	N	Mean (SD)	
Sanli, 2012[79]	RVMPI/RIMP	NA (all patients had RHC)	mPAP ≥25 mmHg, PCWP ≤15 mmHg	30	0.30 (0.10)	20	0.22 (0.03)	<0.001
Children with unrepaired CHD with or without PAH and healthy controls (N=70)	TAPSE			30	1.90 (0.24)	20	2.42 (0.21)	<0.0001
	RVD/RV size			30	4.40 (0.74)	20	4.15 (0.62)	>0.05
Fair								
Takatsuki, 2012[82]	RVDd	NA (case-control design; 88% had RHC)	mPAP ≥25 mmHg, PCWP ≤15 mmHg	51	23.5 (6.0)	51	18.1 (4.9)	<0.001
Children with iPAH (N=51) and healthy controls (N=51) (total N=102)	RVMPI			51	0.63 (0.30)	51	0.21 (0.10)	<0.001
	TRV			51	4.1 (0.8)	51	2.2 (0.2)	<0.001
Fair	S'			51	11.3 (2.4)	51	13.6 (2.8)	<0.001
Ruan, 2007[56]	TRV/VTI_{RVOT}	NA (case-control design)	NR	70	0.66 (0.13)	35	0.13 (0.11)	<0.01
Known PAH and healthy controls (N=180)								
Fair								
Frea, 2011[35a]	FAC	TRV≥3m/s or sPAP≥40mmHg	mPAP ≥25 mmHg, PCWP ≤15 mmHg	4	41.25 (2.22)	34	43.7 (4.5)	0.29
SSc patients with no signs or symptoms of PAH (N=76)	RIMP	TRV ≥3 m/s or sPAP ≥40 mmHg	mPAP ≥25 mmHg, PCWP ≤15 mmHg	4	0.32 (0.16)	34	0.26 (0.07)	0.14
Fair	RV size	TRV ≥3 m/s or sPAP ≥40 mmHg	mPAP ≥25 mmHg, PCWP ≤15 mmHg	4	35.2 (30)	34	33 (3.5)	0.24
	TRV/VTI_{RVOT}	TRV ≥3 m/s or sPAP ≥40 mmHg	mPAP≥25mmHg, PCWP≤15mmHg	4	0.157 (0.033)	34	0.122 (0.022)	0.01
Frea, 2011[35a]	TAPSE	TRV ≥3 m/s or sPAP ≥40 mmHg	mPAP ≥25 mmHg, PCWP ≤15 mmHg	4	23 (1.63)	34	22.3 (2.19)	0.54
SSc patients with no signs or symptoms of PAH (N=76)								
Fair								

Table 10. Echocardiographic parameter values by diagnostic group (continued)

Study Population (N) Quality	Echocardio-graphic Parameter	Criteria for Verification by RHC	Reference Diagnostic Criterion	Patients With PAH		Patients Without PAH		P-value
				N	Mean (SD)	N	Mean (SD)	
Allanore, 2008[27a] SSc patients with echocardiography sPAP <40 mmHg and no NYHA III/IV symptoms (N=101) Good	sPAP	sPAP >40 mmHg, DLCO <50% predicted without pulmonary fibrosis or unexplained dyspnea, negative CT, D-dimer	mPAP ≥25 mmHg, PCWP ≤15 mmHg	8	38.2 (9.4)	93	31.2 (5.9)	0.001
Nakayama, 1998[48b] Patients with known, symptomatic CTEPH or PPH (N=35) Fair	mPAP	NA (all patients had RHC)	NR but includes negative V/Q scan	19	41 (10)	16	54 (9)	

CTEPH = chronic thromboembolic pulmonary hypertension; DLCO = diffusion capacity of the lung for carbon monoxide; iPAH = idiopathic pulmonary arterial hypertension; mmHg = millimeter of mercury; mPAP = mean pulmonary artery pressure; MPI = myocardial performance index; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PAH = pulmonary arterial hypertension; PH = pulmonary hypertension; PPH = primary pulmonary hypertension; PVR = pulmonary vascular resistance; RA = right atrium; RHC = right heart catheterization; RIMP = right index of myocardial performance; RV = right ventricle; RVD = right ventricular dysfunction; RVDd = right ventricular dysfunction (diastolic); RVDs = right ventricular dysfunction (systolic); sPAP = systolic pulmonary artery pressure; SD = standard deviation; SSc = systemic sclerosis; TRV = tricuspid regurgitant jet velocity; V/Q = ventilation perfusion scan; VSD = ventricular septal defect; VTI_{RVOT} = velocity-time integral of right ventricular outflow tract

[a]Studies that assessed baseline NT-proBNP as predictors of future development of PAH.

[b]Study attempted to distinguish primary PAH from CTEPH (rather than no PAH).

In the two studies that examined echocardiographic predictors of later development of PAH, TRV/VTI_{RVOT} and sPAP at baseline showed statistically significant differences among those who later developed PAH compared with those who did not (Table 10). Other parameters examined, including FAC, RIMP, RV size and TAPSE, failed to show statistically significant differences; however, the number of cases in this study was small (n=4), suggesting this analysis lacks sensitivity. Likewise the number of parameters examined for association is large relative to the number of cases, suggesting the possibility of finding significant associations by chance.

Thirteen studies evaluated concurrent echocardiography measurement with diagnosis of PAH and provided data on seven different echocardiographic parameters: sPAP (or TRV), RIMP, RV size, RA size, S', TAPSE, TRV/VTI_{RVOT} and FAC. Seven of the studies used a case-control design; four used elevated sPAP by echocardiography to select patients for diagnostic verification; three studies verified all participants' diagnosis with RHC:

- For FAC, three case-control studies showed reasonably large differences, statistically significant in both studies that reported a statistical comparison.
- For RA size, findings in two studies were inconsistent: one case-control study reported statistically significant differences, but a cohort study found no difference.
- For RIMP, all six studies reported statistically significant differences.
- For RV size, three of eight studies reported statistically significant differences, four did not detect a difference, and one study did not report a statistical test for differences.
- For S', four of five studies reported statistically significant differences.
- For TAPSE, two of three studies reported statistically significant differences.
- For TRV/VTI_{RVOT} or the related $sPAP/VTI_{RVOT}$, both studies showed statistically significant differences.

Four studies indicated large differences in echocardiography sPAP between patients with PAH and those without PAH with differences in means ranging from 18 to 52 mmHg. These differences, while highly significant, reflect incorporation bias since the diagnostic classification is based on mPAP, which is highly correlated with sPAP.

Accuracy and Precision of Echocardiography Versus RHC

Twenty-eight studies reported the correlation or agreement between echocardiographic measurements and corresponding hemodynamic parameters measured at RHC (Table 11). The correlation coefficient between echocardiography sPAP and RHC sPAP ranged from 0.15 to 0.96. Two studies reported correlation of echocardiography sPAP with both simultaneous and nonconcurrent RHC; in each case, correlations were improved when echocardiography was performed simultaneously with RHC; however, the improvement in correlation was only 0.03 to 0.06.

Table 11. Correlation of echocardiographic parameters with RHC in PAH

Study Population (N) Quality	Echocardio-graphic Parameter	Measurement Details	RHC Parameter	Total N (N Not Estimable)	Correlation (p-Value)	Bias (SD)
Fukuda, 2011[72] Patients with known PH (N=67) Fair	FAC	(RV end-diastolic area – RV end-systolic area) / RV end-diastolic area * 100%	mPAP PVR (Fick)	45 45	-0.47 (0.001) -0.46 (0.002)	
Selimovic, 2007[57] Patients with suspected pulmonary vascular disease; 37 of 42 NYHA III/IV (N=42) Good	mPAP mPAP sPAP	PADP + 0.33(PASP – PADP) Simultaneous with RHC $4 * TRV^2 + RAP$ (5, 10, 15)	mPAP mPAP sPAP	56 (4) 20 (0) 56 (4)	0.91 (0.04) 0.95 (0.31) 0.88 (0.3)	-2.0 (7.2) 1.4 (5.8) -1.7 (12.3)
Tian, 2011[62] Suspected PH based on symptoms (N=42) Fair	mPAP		mPAP	42 (0)	0.88(0.0001)	-5.7 (0.84)
Vonk, 2007[66] Connective tissue diseases; one-third NYHA III/IV (N=98) Fair	RIMP		mPAP	35 (2)	0.46 (0.01)	
Fukuda, 2011[72] Patients with known PH (N=67) Fair	RIMP		mPAP PVR (Fick)	45 (0) 45 (0)	-0.21 (0.174) -0.26 (0.12)	

Table 11. Correlation of echocardiographic parameters with RHC in PAH (continued)

Study Population (N) Quality	Echocardio-graphic Parameter	Measurement Details	RHC Parameter	Total N (N Not Estimable)	Correlation (p-Value)	Bias (SD)
Vonk, 2007[66] Connective tissue diseases; one-third NYHA III/IV (N=98) Fair	RIMP		PVR (TD)	35 (2)	0.33 (0.08)	
Fukuda, 2011[72] Patients with known PH (N=67) Fair	RIMP		PVR (Fick)	45 (0)	-0.26 (0.12)	
Cevik, 2012[74] Children with CHD (N=30) and healthy controls (N=40) (total N=70) Fair	RVMPI		sPAP mPAP	30 (NR) 30 (NR)	0.54 (0.002) 0.53 (0.003)	
Fukuda, 2011[72] Patients with known PH (N=67) Fair	S'		mPAP PVR (Fick)	45 (0) 45	-0.39 (0.009) -0.41 (0.013)	
Dahiya, 2010[31] Referred for evaluation of suspected PH; all patients had dyspnea (N=114) Good	TRV/VTI_{RVOT}		PVR (TD)	50	0.77 (0.001)	1.8 (3.3)
Lindqvist, 2011[41] Patients with PH undergoing RHC (N=30) Fair	TRV/VTI_{RVOT}		PVR (TD)	25 (5)	0.78 (0.001)	6.1 (4.0)

Table 11. Correlation of echocardiographic parameters with RHC in PAH (continued)

Study Population (N) Quality	Echocardio-graphic Parameter	Measurement Details	RHC Parameter	Total N (N Not Estimable)	Correlation (p-Value)	Bias (SD)
Rajagopalan, 2009[52] Known pulmonary hypertension (N=52) Fair	TRV/VTI_{RVOT}		PVR (Fick)	52	0.73 (0.001)	0 (4.3)
Roule, 2010[55] Known PH (N=37) Good	TRV/VTI_{RVOT}		PVR (TD)	37 (NR)	0.76 (0.0001)	0 (1.9)
Vlahos, 2008[65] Known or suspected pulmonary hypertension (N=12) Poor	TRV/VTI_{RVOT}		PVR (Fick)	12 (0)	0.843 (NR)	
Ajami, 2011[69] Children & young adults with congenital heart disease referred for RHC (N=20) Good	TRV/VTI_{RVOT}		PVR (Fick)	20 (0)	0.73 (NR)	
Rajaram, 2012[77] CTD suspected of PH based on symptoms or screening tests (N=81) Fair	TG	$4 * TRV^2$	mPAP PVR	81 (NR) 81 (NR)	0.84 (0.001) 0.76 (0.001)	

Table 11. Correlation of echocardiographic parameters with RHC in PAH (continued)

Study Population (N) Quality	Echocardio-graphic Parameter	Measurement Details	RHC Parameter	Total N (N Not Estimable)	Correlation (p-Value)	Bias (SD)
Arcasoy, 2003[83] Advanced lung disease, undergoing evaluation for lung transplantation (N=374) Good	sPAP	4 * TRV^2 + RAP	sPAP	166 (208)	0.69 (<0.0001)	
Denton, 1997[32] SSc patients suspected of PAH, most due to reduced DLCO (N=93) Fair	sPAP	4 * TRV^2 + JVP	sPAP	20 (13)	0.83 (0.001)	11.4 (9.8)
Farber, 2011[9] Patients with PAH (N=1883) Fair	sPAP	4 * TRV^2 + RAP	sPAP	1360 (NR)	0.56 (0.001)	
Hammerstingl, 2012[76] Patients with PH undergoing RHC (N=155) Fair	sPAP sPAP		mPAP sPAP	155 (NR)	0.43 (<0.0001) 0.15 (0.06)	
Hsu, 2008[37] SSc patients with dyspnea or other clinical features suggestive of PAH (N=49) Good	sPAP	4 * TRV^2 + 10	sPAP	49 (NR)	0.71 (NR)	

Table 11. Correlation of echocardiographic parameters with RHC in PAH (continued)

Study Population (N) Quality	Echocardio-graphic Parameter	Measurement Details	RHC Parameter	Total N (N Not Estimable)	Correlation (p-Value)	Bias (SD)
Fisher, 2009[33] Patients undergoing RHC for known or suspected PAH; symptoms not described (N=65) Good	sPAP	4 * TRV^2 + RAP	sPAP	59 (NR)	0.66 (0.001)	-0.6 (20)
Kovacs, 2010[40] Patients with CVD some with symptoms (N=52) Good	sPAP	4 * TRV^2 + RAP	sPAP	28 (9)		0.3 (7.6)
Nogami, 2009[49] Suspected pulmonary hypertension; all patients symptomatic (N=29) Good	sPAP	4 * TRV^2 + RAP (5, 15)	sPAP	20 (0)	0.86 (0.01)	-5.9 (14.1)
Rich, 2011[53] Patients with both RHC and Doppler echo (N=183) Good	sPAP	4 * TRV^2 + RAP (5, 10, 15 or 20) With simultaneous RHC	sPAP sPAP	160 (EXCL) 23 (EXCL)	0.68 (0.001) 0.71 (0.01)	2.2 (18.6) 8.0 (8.8)
Roeleveld, 2005[54] Known PH (N=47) Fair	sPAP	4 * TRV^2 + RAP (5, 10, 15) With simultaneous RHC	sPAP sPAP	35 (9) 22 (1)	0.375 (0.026) 0.94 (0.69)	-5 (30.1) 0.7 (7.8)
Selby, 2012[80] HIV-infected patients (N=422) Fair	sPAP	4 * TRV^2 + RAP	sPAP	76 (NR)	0.49 (<0.0001)	1.75 (7.0)

Table 11. Correlation of echocardiographic parameters with RHC in PAH (continued)

Study Population (N) Quality	Echocardio-graphic Parameter	Measurement Details	RHC Parameter	Total N (N Not Estimable)	Correlation (p-Value)	Bias (SD)
Tian, 2011[62] Suspected PH based on symptoms (N=42) Fair	sPAP	4 * TRV^2 + RAP (4, 10, 14)	sPAP	42 (EXCL)	0.96 (0.0001)	-1.8 (1.8)
Vonk, 2007[66] Connective tissue diseases. One-third NYHA III/IV (N=98) Fair	sPAP	4 * TRV^2 + RAP	sPAP	35 (0)	NR (0.001)	
Willens, 2008[67] Patients with known PH and elevated sPAP and controls with CHF and elevated sPAP (N=47) Fair	sPAP	4 * TRV^2 + RAP	sPAP	44 (3)	0.75 (0.001)	
Rajagopalan, 2009[52] Known pulmonary hypertension (N=52) Fair	sPAP S' S' S'	4 * TRV^2 + RAP	sPAP PVR (Fick) CO TG	32 (0)	0.87 (0.001) -0.79 (<0.0001) 0.78 (<0.001) 0.72 (<0.001)	
Murata, 1997[47] SSc patients. Symptoms not described, but most had reduced DLCO (N=135) Fair	sPAP	4 * TRV^2 + 10	sPAP	19 (6)	0.41 (NR)	-0.53 (12.1)

Table 11. Correlation of echocardiographic parameters with RHC in PAH (continued)

Study Population (N) Quality	Echocardio-graphic Parameter	Measurement Details	RHC Parameter	Total N (N Not Estimable)	Correlation (p-Value)	Bias (SD)
Fukuda, 2011[72] Patients with known PH (N=67) Fair	TAPSE	Total excursion of tricuspid annulus during systole	mPAP PVR (Fick)	45 (0) 45 (0)	-0.33 (0.027) -0.49 (0.002)	
Condliffe, 2011[30] SSc patients with suspected PAH; symptoms not described (N=89) Fair	TRV TRV	$4 * TRV^2$ $4 * TRV^2$	mPAP PVR (TD)	70 (0) 70 (0)	0.64 (0.001) 0.76 (0.001)	
Fisher, 2009[33] Patients undergoing RHC for known or suspected PAH; symptoms not described (N=65) Good	TRV CO	$4 * TRV^2$	sPAP CO (TD)	59 (NR) 65 (NR)	 0.74 (<0.001)	-1.8 (18.1) -0.1 (1.2)
Fonseca, 2011[34] Sickle cell disease; symptoms not described (N=80) Fair	TRV	$4 * TRV^2$	sPAP	26 (0)	0.77 (0.001)	
Mourani, 2008[45] Children under 2 years of age undergoing RHC for chronic lung disease (N=25) Fair	TRV	$4 * TRV^2$	sPAP	19 (12)	0.19 (0.43)	

Table 11. Correlation of echocardiographic parameters with RHC in PAH (continued)

Study Population (N) Quality	Echocardio-graphic Parameter	Measurement Details	RHC Parameter	Total N (N Not Estimable)	Correlation (p-Value)	Bias (SD)
Mukerjee, 2004[46] SSc patients with suspected PAH, symptoms of exercise limitation and reduced DLCO (N=137) Fair	TRV	TG calculated from TRV using "standard templates"	sPAP	137 (NR)	0.67 (NR)	
Roule, 2010[55] Known PH (N=37) Good	TRV	$4 * TRV^2$	sPAP	37 (0)	0.8 (NR)	

CO = cardiac output; EXCL = excluded from study; JVP = jugular venous pressure; mPAP = mean pulmonary artery pressure; MPI = myocardial performance index; NR = not reported; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PAH = pulmonary arterial hypertension; PADP = pulmonary artery diastolic pressure; PASP = pulmonary artery systolic pressure; PH = pulmonary hypertension; PPH = primary pulmonary hypertension; PVR = pulmonary vascular resistance; RAP = right atrial pressure; RHC = right heart catheterization; RIMP = right index of myocardial performance; RV = right ventricle; SD = standard deviation; sPAP = systolic pulmonary artery pressure; SSc = systemic sclerosis;
TAPSE = tricuspid annular plane systolic excursion; TG = tricuspid gradient; TRV = tricuspid regurgitant jet velocity; VSD = ventricular septal defect; VTI_{RVOT} = velocity-time integral of right ventricular outflow tract

Bias in measurement was estimated by examining the difference between two tests measured on the same scale using the method of Bland and Altman. In nine studies comparing sPAP values, the average bias varied between a 5.9 mmHg underestimate and an 11.4 mmHg overestimate by echocardiography. The standard deviation of the bias measurements ranged from 1.8 to 30.1, with a median of 9.3. With a standard deviation of this magnitude, one would expect about 70 percent of echocardiography sPAP readings to fall within 10 mmHg of RHC sPAP; however, the large REVEAL registry[9] found that only 39.8 percent of echocardiographic estimates of sPAP were within 10mmHg of same-day RHC-measured sPAP, corresponding to a standard deviation of approximately 19 mmHg. The remaining 60 percent were approximately equally divided between overestimates (greater than 10 mmHg) and underestimates (greater than 10 mmHg). Three additional studies reported the percentage of patients in which echocardiography sPAP and RHC sPAP readings were within 10 mmHg of each other. Two studies found this to be 48 percent,[33,83] which would suggest a standard deviation of approximately 15 mmHg. The third study reported 80 percent,[80] which would suggest a standard deviation of approximately 7.8. In one study, divergence between echocardiography and RHC was greater than 20 mmHg in 28 percent of patients and greater than 30 mmHg in 9 percent of patients,[83] both suggesting a standard deviation of approximately 18. These estimates assume a normal distribution and a bias of zero (Table 12).

Table 12. Further data on accuracy of echocardiographic estimates of sPAP compared with RHC, described as percentage of patients within a specified threshold

Study	Percentage of Echocardiographic Estimates Within Threshold			Standard Deviation	
	10 mmHg	20 mmHg	30 mmHg	Estimated	Reported
Farber, 2011[9]	39.8%	–	–	19.2	NR
Fisher, 2009[33]	48%	–	–	15.4	20
Arcasoy, 2003[83]	48%	–	–	15.4	NR
	–	72%	–	18.5	NR
	–	–	91%	17.6	NR
Selby, 2012[80]	80%	–	–	7.8	7.0

mmHg = millimeter of mercury; NR = not reported

Four studies reported correlation between echocardiography transtricuspid gradient and sPAP, with estimates ranging from 0.19 to 0.80. The low outlier was a small study of young children with chronic lung disease. One other study found negligible bias but a large standard deviation of difference between echocardiography and RHC measures.[33] Two additional studies correlated TG and mPAP with estimates of 0.64 and 0.84, respectively.[30,77]

Six studies correlated TRV/VTI_{RVOT} with PVR by RHC. Correlation coefficients indicated strong correlation ranging from 0.73 to 0.84, with bias ranging from 0 to 6.1, and standard deviations ranging from 1.9 to 4.3 Wood units.

Two studies reported strong correlations between echocardiographic estimates of mPAP with RHC-measured mPAP. Correlation coefficients were 0.88 and 0.91 but increased to 0.95 when echocardiography was simultaneous with RHC. The estimates of bias of a 2 and 5.7 mmHg underestimate improved to a 1.4 mmHg overestimate when echocardiography was performed simultaneously with RHC; the standard deviations of difference between echocardiography and RHC ranged from 0.84 to 7.2.

Low to moderate correlations were observed between RIMP and mPAP, RIMP and PVR, TAPSE and mPAP, FAC and mPAP, and FAC and PVR. Two studies found a strong correlation between TG and PVR.[30,77]

Two studies correlated S' with RHC hemodynamic measures and reported moderate to strong correlation of S' with PVR (Fick), CO, and TG.[52,72]

Summary Strength of Evidence for KQ 1

Results for these outcomes and comparisons, along with ratings for strength of evidence are shown in Tables 13–16.

Table 13. Summary strength of evidence for KQ 1: Echocardiography sPAP with NT-proBNP versus echocardiography sPAP in symptomatic patients

Parameter	Number of Studies (Patients)	Domains				Strength of Evidence Effect Estimate (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Sensitivity	1 (121)	High	NA	Direct	Imprecise	**SOE = Insufficient** NT-proBNP >80 pg/mL has a low false-negative rate compared with RHC reference standard; the serial testing study design did not allow for NT-proBNP testing to improve sensitivity beyond that of echo sPAP alone
Specificity	1 (121)	Moderate	NA	Direct	Imprecise	**SOE = Low** NT-proBNP ≤80 pg/mL ruled out PAH in 9–16% of patients with elevated echo sPAP ≥36 mmHg
Correlation	0 (0)	NA	NA	NA	NA	**SOE = Insufficient** NA
Adverse effects	0 (0)	NA	NA	NA	NA	**SOE = Insufficient** NA

CI = confidence interval; echo = echocardiography; NA = not applicable; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PAH = pulmonary arterial hypertension; RHC = right heart catheterization; SOE = strength of evidence; sPAP = systolic pulmonary artery pressure

Table 14. Summary strength of evidence for KQ 1: NT-proBNP compared with RHC

Parameter	Number of Studies (Patients)	Domains				Strength of Evidence Effect Estimate (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Sensitivity	3 (198)	Moderate	Inconsistent	Indirect	Imprecise	**SOE = Low** Range 56% to 100% NT-proBNP has variable sensitivity for diagnosing PAH; uncertain performance for ruling out PAH
Specificity	3 (198)	Moderate	Inconsistent	Indirect	Imprecise	**SOE = Low** Range 24% to 95% NT-proBNP has variable specificity; uncertain performance for ruling in PAH
Correlation	3 (176)	Moderate	Consistent	Indirect	Imprecise	**SOE = Moderate** Range 0.43 to 0.72 Correlation of NT-proBNP and RHC is only moderate
Adverse effects	0 (0)	NA	NA	NA	NA	**SOE = Insufficient** NA

CI = confidence interval; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PAH = pulmonary arterial hypertension; RHC = right heart catheterization; SOE = strength of evidence

Table 15. Summary strength of evidence for KQ 1: TRV/TG/sPAP compared with RHC

Parameter	Number of Studies (Patients)	Domains				Strength of Evidence Effect Estimate (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Sensitivity	19 (2459)	Moderate	Consistent	Indirect	Imprecise	**SOE = Moderate** Range 58% to 100% Echocardiographic estimate of sPAP showed variable sensitivity, with lower prevalence studies finding higher sensitivity
Specificity	19 (2459)	Moderate	Consistent	Indirect	Imprecise	**SOE = Moderate** Range 50% to 98% Echocardiographic estimate of sPAP showed variable specificity, with lower prevalence studies finding higher specificity
Correlation	23 (4217)	Low	Inconsistent	Indirect	Imprecise	**SOE = Moderate** Range 0.38 to 0.96 Echocardiographic estimate of sPAP showed moderate to strong correlation with RHC and were on average unbiased, but were limited by imprecision and by a significant minority of patients in whom TRV was not measurable
Adverse effects	0 (0)	NA	NA	NA	NA	**SOE = Insufficient** NA

CI = confidence interval; PAH = pulmonary arterial hypertension; RHC = right heart catheterization; SOE = strength of evidence; sPAP = systolic pulmonary artery pressure; TG = tricuspid gradient; TRV = tricuspid regurgitant jet velocity

Table 16. Summary strength of evidence for KQ 1: TRV/VTI_{RVOT} compared with RHC

Parameter	Number of Studies (Patients)	Domains				Strength of Evidence Effect Estimate (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Sensitivity	6 (196)	Moderate	Consistent	Indirect	Precise	**SOE = Moderate** Range 89% to 100% Echocardiographic estimate of PVR showed reasonably high sensitivity for ruling in PAH
Specificity	6 (196)	Moderate	Consistent	Indirect	Imprecise	**SOE = Moderate** Range 50% to 97% Echocardiographic estimate of PVR showed variable specificity, with better specificity in lower prevalence studies (range, 94% to 97%)
Correlation	6 (196)	Low	Consistent	Indirect	Precise	**SOE = High** Range 0.74 to 0.84 Strong correlation between echocardiographic estimates of PVR and PVR by RHC
Adverse effects	0 (0)	NA	NA	NA	NA	**SOE = Insufficient** NA

CI = confidence interval; PAH = pulmonary arterial hypertension; PVR = pulmonary vascular resistance; RHC = right heart catheterization; SOE = strength of evidence; TRV = tricuspid regurgitant jet velocity; VTI_{RVOT} = velocity-time integral of right ventricular outflow tract

KQ 2: Management of PAH

For patients with PAH, what are the comparative effectiveness and safety of (a) echocardiography versus biomarkers and (b) echocardiography versus echocardiography plus biomarkers in managing PAH and on intermediate-term (≤90 days) and long-term (>90 days) patient outcomes ?

Key Points

- No data are available regarding the comparative effectiveness of echocardiography versus biomarkers or echocardiography versus echocardiography plus biomarkers in the management of PAH or patient outcomes (insufficient strength of evidence).
- Systolic pulmonary artery pressure (sPAP) estimated by echocardiography shows good correlation with sPAP from RHC (low strength of evidence).
- Serum brain natriuretic peptide (BNP) level shows only moderate correlation with these RHC measures: mean pulmonary artery pressure (mPAP) (moderate strength of evidence), pulmonary vascular resistance (low strength of evidence), right atrial pressure (moderate strength of evidence), cardiac index (low strength of evidence), and clinical outcomes such as the 6-minute walk distance (6MWD) test (moderate strength of evidence).
- BNP level shows poor correlation with RHC pulmonary capillary wedge pressure (PCWP) (low strength of evidence).

- BNP level alone is not an accurate surrogate marker for disease severity (high strength of evidence).
- Increase in level of log-transformed BNP is a strong predictor of mortality (moderate strength of evidence).
- Presence of pericardial effusion is also a strong predictor of mortality although there was wide variability in results for this measure (moderate strength of evidence).
- Right atrial (RA) size correlates with increased risk of mortality (moderate strength of evidence).
- Fractional area change (FAC) is a poor predictor of mortality, but results are variable across studies (moderate strength of evidence).
- Serum uric acid level appears to predict mortality (low strength of evidence)
- Tricuspid annular plane systolic excursion (TAPSE) has inconsistent association with mortality (insufficient strength of evidence).
- We found no studies addressing diagnostic thinking efficacy, therapeutic efficacy, or harms (insufficient strength of evidence).

Description of Included Studies

We identified 99 unique studies involving a total of 8655 patients that evaluated the use of biomarkers or echocardiographic parameters in the management of PAH or as predictors of patient outcomes.[6,43,58,68,84-178] Of these studies, 68 were rated good quality, 29 fair quality, and 2 poor quality. Biomarkers evaluated were natriuretic peptides, endothelin-1, uric acid, troponin T, nitric oxide, asymmetric dimethylarginine, cyclic guanosine monophosphate, and D-dimer. Echocardiographic parameters evaluated were right ventricular (RV) size, RA size, FAC, TAPSE, right ventricular index of myocardial performance (RIMP), myocardial performance index (MPI), Tei index, sPAP, mPAP, tricuspid regurgitation (TR) jet, tricuspid regurgitation jet velocity/velocity-time integral right ventricular outflow tract (TRV/VTI_{RVOT}), right ventricular ejection fraction (RVEF), right ventricular systolic pressure (RVSP), and pericardial effusion. We found no studies addressing diagnostic thinking efficacy or therapeutic efficacy.

Study Characteristics

Table F-2 in Appendix F summarizes the study location, patient population, study size, sex ratio, index test, comparator, type of result reported, and the quality for each study relevant to KQ 2. Of the 95 studies that reported sex, there were a total of 3972 women and 1618 men. Of the 93 studies that reported age, 72 studies included adults,[6,58,68,84,85,88-94,96,97,100-104,106-121,124,125,127,128,130-134,137,139-145,147-152,154,156,157,159,160,162,164,166,167,170,171,174,175,178] 9 studies included children,[87,98,122,129,136,153,172,173,177] and 12 studies included both adults and children.[86,99,105,138,146,158,161,163,165,168,169,176] Study locations included Asia (23 studies), Europe (36), United States or Canada (29), Africa (1), Australia/New Zealand (1), South America (1), multiple geographic locations (3), and unreported or unclear setting (5).

We did not find any studies that assessed the comparative effectiveness of echocardiography versus biomarkers or echocardiography versus echocardiography plus biomarkers as outlined in our original Key Question. We did find one recent validation study by Benza et al.[179] of a PAH risk calculator that incorporates biomarkers, echocardiographic findings, and clinical assessment to predict survival. Previously, this team had developed the risk calculator based on known prognosticators of survival in patients with PAH. These variables include World Health Organization subgroup demographics (sex and age), renal disease, functional class, vital signs,

6MWD test, BNP level, presence of pericardial effusion, pulmonary function tests, and findings on RHC, each of which were assigned point values based on presence or level. This recent study validated the risk calculator using prospectively collected independent data from patients with newly diagnosed class I PAH and showed good discriminatory ability. This was the only predictive model we found that both incorporated multiple risk factors, including biomarkers and echocardiographic parameters, and was prospectively validated. However, this report does not permit the assessment of the combination of biomarker and echocardiographic data compared with other routine clinical assessment alone.

Because of the lack of data directly addressed in the key question, we instead focus the remainder of this section on the available studies that evaluate the ability of echocardiography or biomarkers to assess the severity of PAH, to predict events such as lung transplantation or death, or to assess a patient's response to therapy. By evaluating the independent association of biomarkers or echocardiography, one can impute the comparative effectiveness via indirect comparison. The most common biomarker evaluated was BNP (59 studies), followed by uric acid (9), endothelin-1 (6), troponin T (4), nitric oxide (2), cGMP (2) and ANP (1). We found no studies assessing D-dimer or asymmetric dimethylarginine to evaluate their ability to assess severity of disease, response to therapy, or outcome.

Thirty-nine studies evaluated several echocardiographic parameters. These included sPAP (17 studies), RIMP/MPI/Tei (14), RA size (11), pericardial effusion (11), RV size (9), FAC (8), mPAP (8), TAPSE (6), TR jet (4), TRV/VTI_{RVOT} (3), RVEF (2), echocardiography-derived cardiac index (2), and RVSP (2).

For the comparators, we focused on RHC hemodynamics, 6-minute walk distance (6MWD), and functional class (FC) as the reference standards for assessing severity of disease. Thirty-four studies used RHC as a reference test, 15 studies used 6MWD as a reference test, and 10 studies used FC as a reference test.

Thirty-nine studies evaluated the correlation between biomarkers and/or echocardiographic parameters and the comparators. Twenty-three studies evaluated hazard ratios (HR) for death, two studies evaluated HR for a composite outcome of death or lung transplant, and one study evaluated HR for lung transplant alone. Twenty-three studies evaluated changes in mean values in response to therapy, and four studies evaluated changes in median values in response to therapy. Eight studies assessed mean or median change from baseline in response to therapy.

Detailed Synthesis

Evaluation of Prognostic Value of Biomarkers and Echocardiography as Assessed by Correlation With Outcomes With Known Prognostic Ability

Table G-1 in Appendix G outlines the 39 studies that reported the correlation between a biomarker or echocardiographic parameter result and a hemodynamic or clinical outcome. The included studies consisted of a total of 1243 patients. Of studies with adults reporting age, the mean age ranged from 37 to 64 years. Two studies evaluating children reported a median age range of 7.0 to 10 years. The following were the most common comparisons encountered in the studies and included in our analysis:

- BNP versus RHC-mPAP (14 studies, 606 patients)
- BNP versus RHC-PVR (13 studies, 684 patients)
- BNP versus RHC-RAP (12 studies, 645 patients)

- BNP versus RHC-CI (10 studies, 550 patients)
- BNP versus 6MWD (9 studies, 437 patients)
- BNP versus RHC-PCWP (5 studies, 319 patients)
- Echocardiography sPAP versus RHC-sPAP (9 studies, 362 patients)

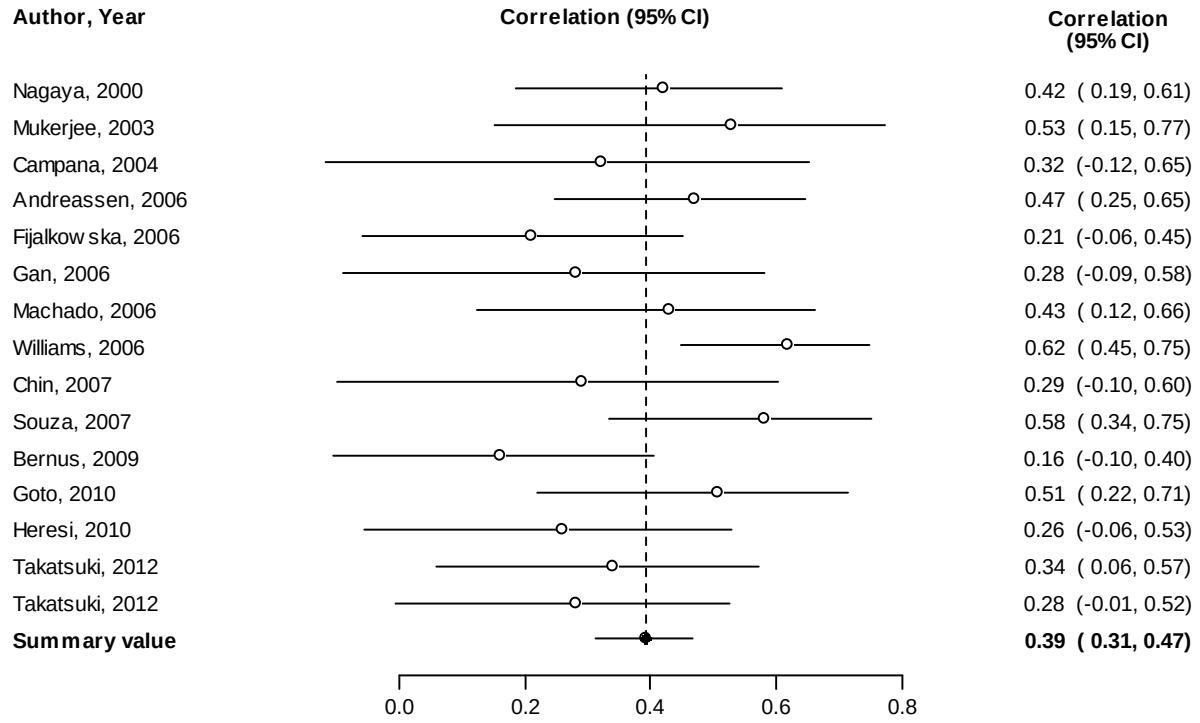
Meta-analysis of Correlation Studies

There appeared to be excessive heterogeneity in correlations that seemed to be explained by temporal differences between noninvasive assessment and outcome measures, whether hemodynamic at RHC or functional assessment. Therefore, we decided to limit our meta-analysis of correlation studies to those assessing correlation between baseline values at a given time. We did not include studies that correlated change in values between two tests due to the small number of these studies. To improve the robustness of the results, we also limited our meta-analysis to those comparisons that were evaluated in at least four studies. One study[177] included data for both BNP and NT-proBNP and so is included twice in several analyses.

BNP Versus RHC-mPAP

Figure 9 shows the forest plot of the correlation between BNP and RHC-mPAP from 14 studies (606 patients) with values ranging from 0.16 to 0.62. The summary correlation coefficient was 0.39 (95% CI, 0.31 to 0.47), indicating moderate correlation between the two tests. There was moderate heterogeneity, with a Q-value of 18.8 for 14 degrees of freedom, I^2=25.52%, p=0.17. In these studies, heterogeneity was introduced in part by different study populations. While all studies evaluated patients with PAH, there was a variety of etiologies included with some studies evaluating a specific etiology[43,68,135,139,148] and others assessing a mixture of PAH etiologies.[84,87,93,95,102,107,110,115,177] In addition, two studies[87,177] focused on a pediatric population while the others focused on adult populations. Further, studies evaluated different BNP measurements, which may add to heterogeneity. Some studies reported results for BNP,[87,93,95,110,115,135] and others reported results for NT-proBNP,[43,68,84,102,107,139,148] while the Takatsuki study reported results for both.[177] Some studies reported log-transformed values,[68,87,93,102,135,139,148] and others reported non–log-transformed values.[43,84,95,107,110,115,177] Most studies included patients receiving a variety of PAH treatments, while the Chin study focused on patients treated with epoprostenol.[95] The strength of evidence is rated moderate based on most studies with low risk of bias, consistent results of an indirect outcome, and precise estimates.

Figure 9. Forest plot of correlation between BNP and RHC-mPAP

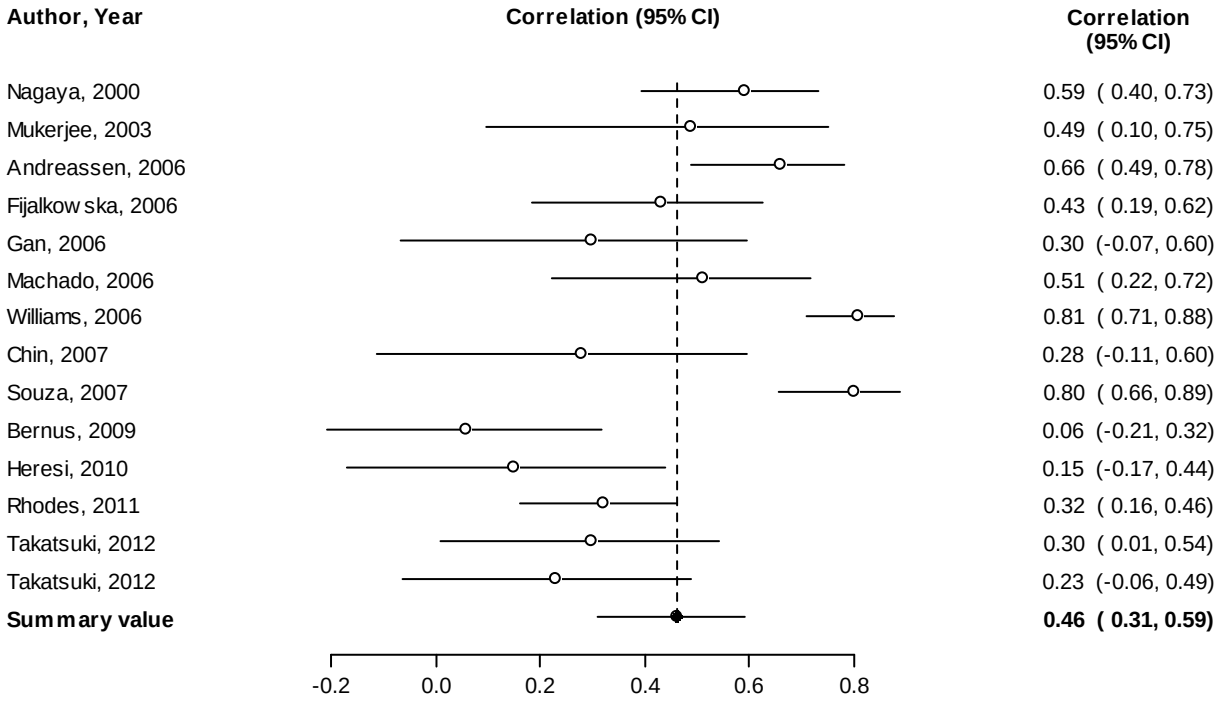


CI=confidence interval

BNP Versus RHC-PVR

Figure 10 shows the forest plot of the correlation between BNP and RHC-PVR from 13 studies (684 patients) with values ranging from 0.06 to 081. The summary correlation coefficient was 0.46 (95% CI, 0.31 to 0.59), indicating moderate correlation between the two tests. There was high heterogeneity, with a Q-value of 71.76 for 13 degrees of freedom, I^2=81.88%, p<0.001. In these studies, heterogeneity was also introduced by different study populations with some studies evaluating a specific etiology,[43,68,135,139,144,148] and others assessing a mixture of PAH etiologies.[84,87,95,102,107,115,177] In addition, two studies[87,177] focused on a pediatric population while the others focused on adult populations. As with the above comparison, studies evaluated different biomarker measurements. Some studies reported results for BNP,[87,95,115,135] and others reported results for NT-proBNP[43,68,84,102,107,139,144,148] while one study reported outcomes for both BNP and NT-proBNP.[177] Some studies reported log-transformed values,[68,87,102,135,139,144,148] and others reported non–log-transformed values.[43,84,95,107,115,177] Further, three studies reported PVR as an index value corrected for body size using cardiac index and PCWP,[87,107,177] while the remainder reported absolute PVR value. The strength of evidence is rated low based on most studies with low risk of bias, inconsistent results of an indirect outcome, and precise estimates.

Figure 10. Forest plot of correlation between BNP and RHC-PVR

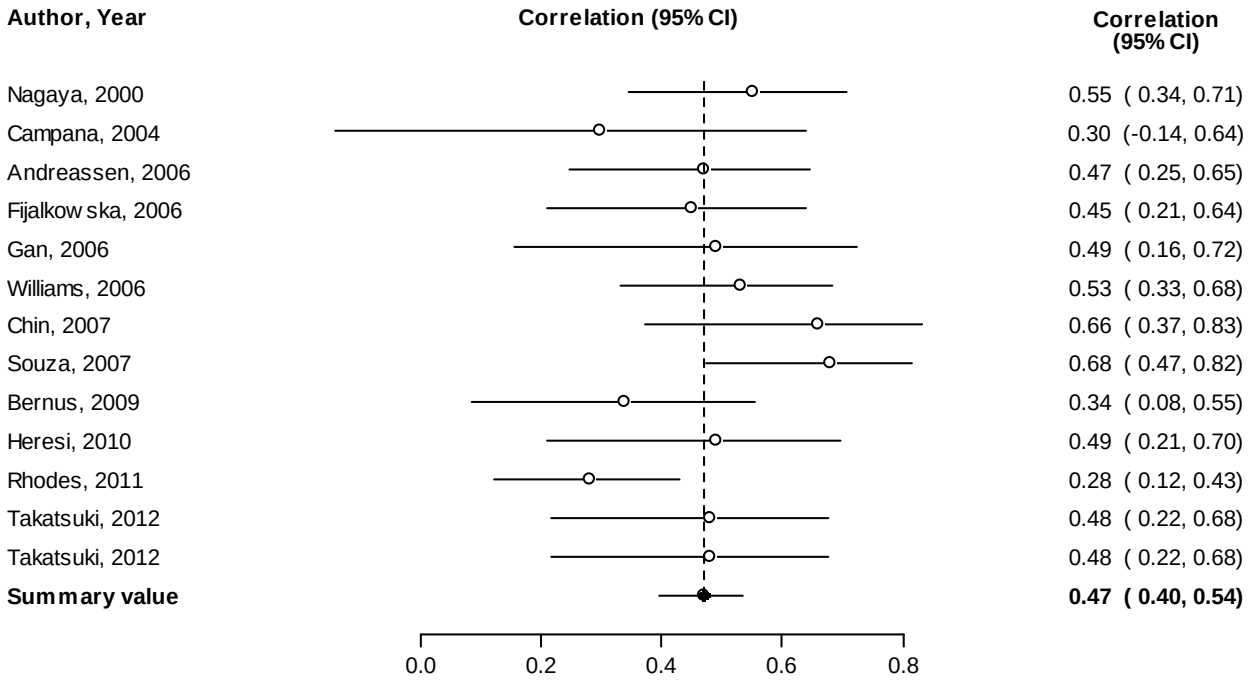


CI = confidence interval

BNP Versus RHC-RAP

Figure 11 shows the forest plot of the correlation between BNP and RHC-RAP from 12 studies (645 patients) with values ranging from 0.28 to 0.68. The summary correlation coefficient was 0.47 (95% CI, 0.40 to 0.54), indicating moderate correlation between the two tests. There was moderate heterogeneity, with a Q-value of 15.5 for 12 degrees of freedom, I^2=22.58%, p=0.22. In these studies, heterogeneity was again introduced by different study populations with a focus on specific PAH etiology in some studies[68,135,144,148] and others evaluating a mixture of PAH etiologies.[84,87,93,95,107,115,177,180] As with the previous comparisons, two studies[87,177] focused on a pediatric population while the others focused on adult populations. Also as before, studies evaluated different biomarker measurements, with some studies reporting results for BNP,[87,93,95,115,135] others reporting results for NT-proBNP,[68,84,102,107,144,148] and the Takatsuki study reporting on both.[177] Some studies reported log-transformed values,[68,87,93,102,135,144,148] and others reported non–log-transformed values.[84,95,107,115,177] The strength of evidence is rated moderate based on all but one study with low risk of bias, consistent results of an indirect outcome, and precise estimates.

Figure 11. Forest plot of correlation between BNP and RHC-RAP

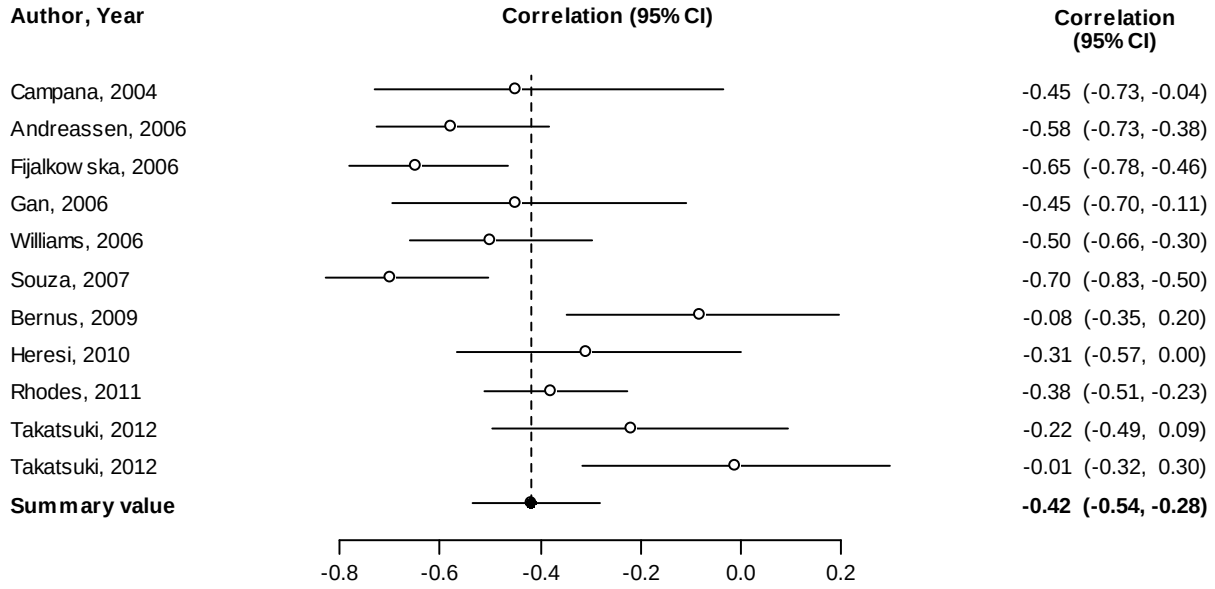


CI = confidence interval

BNP Versus RHC-CI

Figure 12 shows the forest plot of the correlation between BNP and RHC-CI from 10 studies (550 patients) with values ranging from -0.70 to -0.01. The summary correlation coefficient was -0.42 (95% CI, -0.54 to -0.28), indicating negative moderate correlation between the two tests. There was moderate heterogeneity, with a Q-value of 32.60 for 10 degrees of freedom, I^2=69.33%, p<0.001. Again, heterogeneity was likely introduced by different study populations. While all studies evaluated patients with PAH, there was a variety of etiologies included, with some studies looking at a specific etiology,[68,144,148] and others looking at a mixture of PAH etiologies.[84,87,93,102,107,115,177] Two studies[87,177] focused on a pediatric population while the others focused on adult populations. Further, studies evaluated different biomarker measurements. Some studies reported results for BNP,[87,93,115] others reported results for NT-proBNP,[68,84,102,107,144,148] and one reported on both BNP and NT-proBNP.[177] Some studies reported log-transformed values,[68,87,93,102,144,148] and others reported non–log-transformed values.[84,107,115,177] The strength of evidence is rated low based on most studies with low risk of bias, inconsistent results of an indirect outcome, and precise estimates.

Figure 12. Forest plot of correlation between BNP and RHC-CI

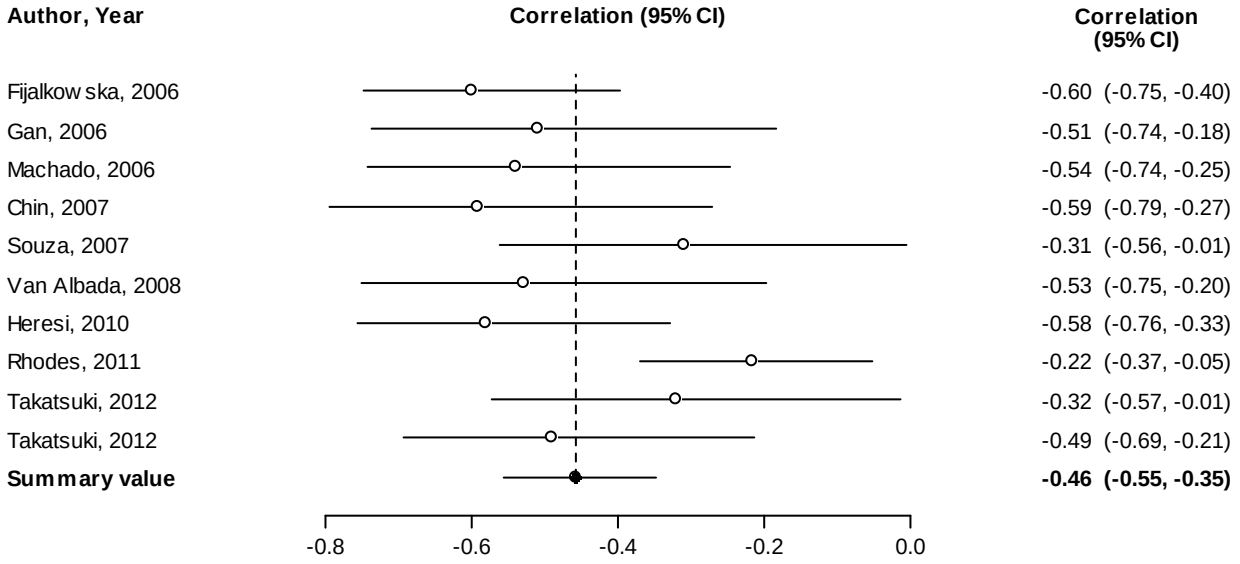


CI=confidence interval

BNP Versus 6MWD

Figure 13 shows the forest plot of the correlation between BNP and 6MWD from 9 studies (484 patients) with values ranging from -0.60 to -0.22. The summary correlation coefficient was -0.46 (95% CI, -0.55 to -0.35), indicating negative moderate correlation between the two tests. There was moderate heterogeneity, with a Q-value of 16.18 for 9 degrees of freedom, I^2=44.37%, p=0.06. The above studies included those that focused on a certain etiology of PAH[43,144,148] or a mixture of PAH etiologies.[95,102,107,115,153] Two studies[153,177] focused on a pediatric population while the others focused on adult populations. Studies evaluated different biomarker measurements. Some studies reported results for BNP,[95,115] others reported results for NT-proBNP,[43,102,107,144,148,153] while one reported on both.[177] Some studies reported log-transformed values,[102,144,148,153] and others reported non–log-transformed values.[43,95,107,115,177] The strength of evidence is rated moderate based on most studies with low risk of bias, inconsistent results of a direct outcome, and precise estimates.

Figure 13. Forest plot of correlation between BNP and 6MWD

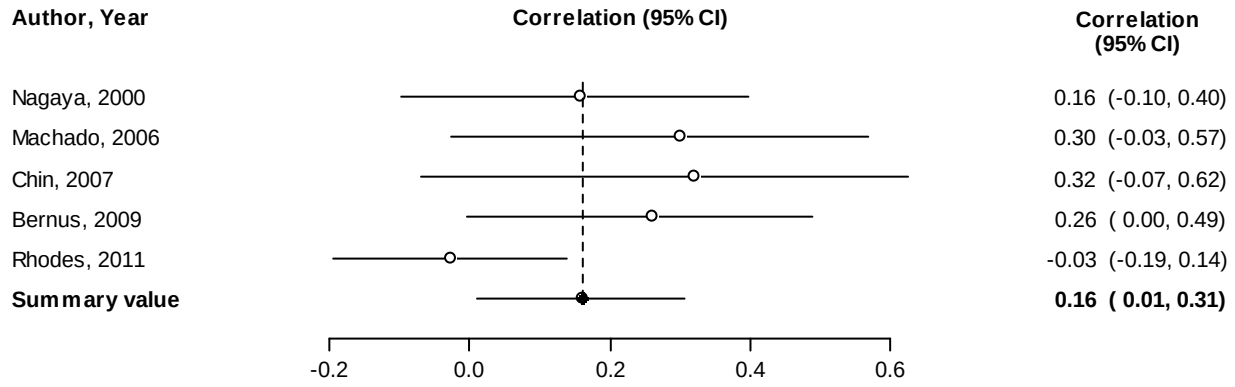


CI = confidence interval

BNP Versus RHC-PCWP

Figure 14 shows the forest plot of the correlation between BNP and RHC-PCWP from 5 studies (319 patients) with values ranging from -0.03 to 0.32. The summary correlation coefficient was 0.16 (95% CI, 0.01 to 0.31), indicating poor correlation between the two tests. There was moderate heterogeneity, with a Q-value of 6.46 for 4 degrees of freedom, I^2=38.04%, p= 0.17. Heterogeneity in this group of studies was also introduced by differing populations, with some studies looking at populations with a specific etiology of PAH,[43,144] some looking at populations with a mixture of PAH etiologies,[135, 369, 595] and the Bernus study[87] focused on a pediatric population. Studies evaluated different BNP values, with some studies reporting results for BNP[87,95,135] and others reporting results for NT-proBNP.[43,144] Some studies reported log-transformed values[87,135,144] and others reported non–log-transformed values.[43,95] There is not enough information in the Rhodes study[144] regarding how variables were measured to adequately explain why this study found a negative correlation between the two markers. The strength of evidence is rated low based on most studies with low risk of bias, consistent results of an indirect outcome, and imprecise estimates.

Figure 14. Forest plot of correlation between BNP and RHC-PCWP

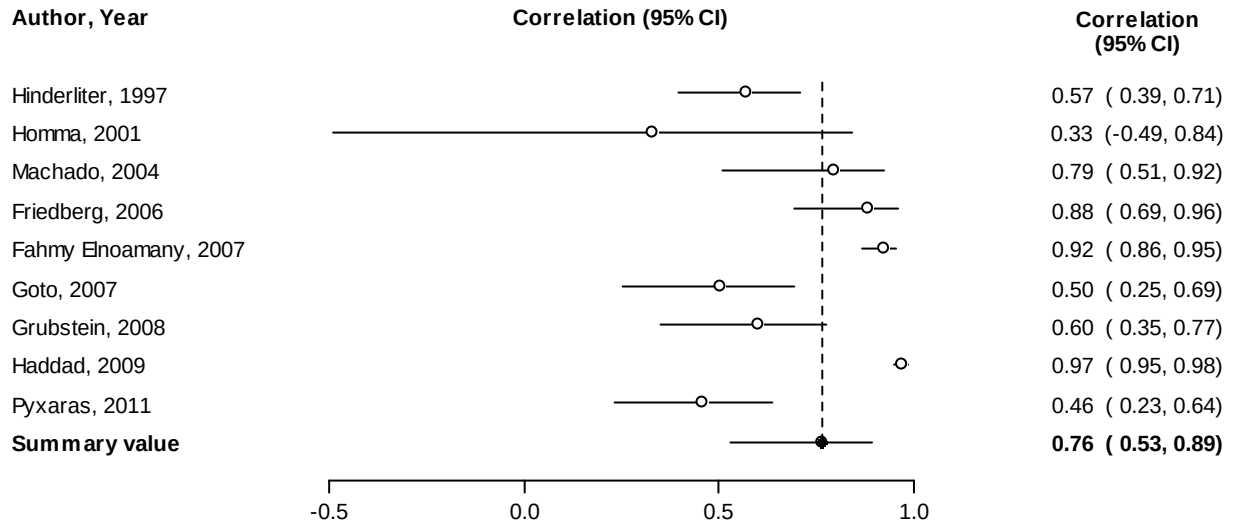


CI=confidence interval

Echocardiography sPAP Versus RHC-sPAP

Figure 15 shows the forest plot of the correlation between echocardiography sPAP and RHC-sPAP from 9 studies (362 patients) with values ranging from 0.33 to 0.97. The summary correlation coefficient was 0.76 (95% CI, 0.53 to 0.89), indicating high correlation between the two tests. There was high heterogeneity, with a Q-value of 110.59 for 8 degrees of freedom, I^2=92.77%, p<0.001. These studies used a variety of methods to estimate sPAP by echocardiography including Bernoulli equation without correction,[100,105,126] Bernoulli equation plus estimated RAP,[110,113,176] and Bernoulli equation plus a fixed value for RAP;[116,118] one study did not report how sPAP was estimated.[112] In addition, there was variability in timing between the catheterization study and the echocardiography study. In three studies it appears that right heart catheterization and echocardiography were done during the initial evaluation.[113,116,118,176] In one study, the tests were done within 30 days of each other[105] and in another done within 4 to 9 months of each other.[126] Two studies were retrospective chart reviews that evaluated the most recent catheterization or echocardiography results,[110,112] and one prospective study did not specify a time frame between the tests.[102] Most studies included patients with a wide range of disease severity, but the Homma study focused only on patients undergoing evaluation for lung transplantation.[118] The strength of evidence is rated low based on most studies with low risk of bias, inconsistent results of an indirect outcome, and precise estimates.

Figure 15. Forest plot of correlation between echocardiography-sPAP and RHC-sPAP



CI = confidence interval

Evaluation of Predictive Value of Biomarkers and Echocardiography as Assessed by Hazard Ratios

Table 17 summarizes the 25 studies that reported the association between a biomarker or echocardiographic parameter and a future clinical outcome in the form of a hazard ratio. Studies evaluating a hazard ratio consisted of 4624 patients, with a female-to-male ratio of 1396 to 517 in those studies reporting sex. Mean age ranged from 33 to 61 years. Included studies evaluated hazard ratios for the following outcomes:

- Mortality (17 studies reporting mean duration of 2 years, one study reporting mean duration of 9 years; 3 studies reporting median duration of 2 years) evaluating BNP (13 studies), pericardial effusion (8), RA size (5), FAC (4), RIMP/MPI/Tei index (5), TAPSE (4), uric acid (4), RV size (2), troponin T (2), peak TRV (2), mPAP (1), sPAP (1), ANP (1)
- Composite outcome of death or lung transplantation (2 studies with one reporting median duration of 4 years and the other reporting mean duration of 3 years) evaluating BNP (1 study), RA size (1), uric acid (1), peak TRV (1), pericardial effusion (1), FAC (1), RV size (1)
- Lung transplantation (one study with mean duration of 2 years) evaluating RA size
- Hospitalization (one study with mean duration of 3.7 years) evaluating BNP and uric acid

Table 17. Hazard ratio table for KQ 2

Study Population (N) Quality	Age (Variability)	Duration of Followup	Index Test	Comparator	N[a]	Result	95% CI	P-value
Benza, 2010[6] Adults with PAH (N=2716) Good	Mean 50.4 (SD 16.8)	Mean followup ~18 mo	Pericardial effusion	Mortality	2105	1.35		0.014
Brierre, 2010[90] Adults with PAH (N=79) Good	Median 61.4 (IQR 46.0 to 74.1)	Mean duration 12 mo	mPAP	Mortality	79	3.94	1.34 to 11.5	0.012
			Pericardial effusion	Mortality	79	5.18	1.85 to 14.5	0.002
			RIMP/MPI/ Tei Index ≥0.98	Mortality	79	5.41	1.12 to 26.1	0.035
			TAPSE	Mortality	79	0.84	0.72 to 0.98	0.024
Bustamante-Labarta, 2002[91] Adults with PPH (N=25) Good	Mean 37.6 (SD 12.7)	Mean followup 29 mo	RA size (RA area)	Transplant (survival from)	25	1.1		0.0004
Fijalkowska, 2006[102] Adults with PH (N=55) Good	Mean 41 (SD 15.1)	Mean followup 770 ± 336 days	FAC	Mortality	55	0.98	0.93 to 1.03	NS
			BNP	Mortality	55	3.0	1.45 to 6.18	0.002
			Pericardial effusion	Mortality	55	3.8	1.46 to 9.93	0.006
			RA size (RA area)	Mortality	55	1.02	0.97 to 1.07	NS
			RIMP/MPI/ Tei index	Mortality	55	1.01	0.34 to 3.01	NS
			RV size (RV diameter)	Mortality	55	1.08	0.99 to 1.17	NS
			cTnT (detectable)	Mortality	55	4.5	1.56 to 12.92	0.005
Forfia, 2006[104] Adults with PH (N=63) Good	Mean 55 (SD 15)	Mean followup 19.3 mo	TAPSE	Mortality	63	1.17	1.04 to 1.32	0.006

Table 17. Hazard ratio table for KQ 2 (continued)

Study Population (N) Quality	Age (Variability)	Duration of Followup	Index Test	Comparator	N[a]	Result	95% CI	P-value
Ghio, 2010[108] Adults with IPAH (N=59) Good	Mean 46.4 (SD 16.1)	Mean followup 52 mo	Pericardial effusion	Mortality	59	0.79	0.18 to 3.4	0.75
			RIMP/MPI/ Tei Index	Mortality	59	2.61	0.52 to 13.03	0.26
			sPAP (transtricuspid gradient)	Mortality	59	0.99	0.98 to 1.02	0.92
			TAPSE	Mortality	59	0.91	0.83 to 0.99	0.026
Hampole, 2009[114] Adults with PH (N=162) Good	Mean 53 (SD 15)	Mean followup 2.1 ± 0.8 yr	BNP (log)	Mortality	162	1.62	1.01 to 2.60	0.044
Heresi, 2010[115] Adults with PPH (N=40) Good	Mean 44 (SD 14)	23.5 ± 13.5 mo	BNP	Mortality	40	1.20	0.11 to 13.28	0.88
Lorenzen, 2011[125] Adults with PAH (N=70) Good	Mean 42 (IQR 48 to 59)	3 mo	BNP (ln)	Mortality	25	1.9	1.2 to 2.9	<0.001
			Uric acid	Mortality	25	1.9	1.5 to 2.6	<0.001
Machado, 2006[43] Patients with sickle cell disease (N=230) Poor	Median 33 (IQR 27 to 44)	Median followup 31 mo	BNP (log) (75^{th} percentile vs. 25^{th} percentile)	Mortality	230	2.1	1.4 to 2.9	<0.001
Mahapatra, 2006[127] Adults with PH (N=54) Fair	Mean 52 (SD 11)	250 person yr	RIMP/MPI/Tei Index	Mortality	54	1.66	1.05 to 2.6	0.04

Table 17. Hazard ratio table for KQ 2 (continued)

Study Population (N) Quality	Age (Variability)	Duration of Followup	Index Test	Comparator	N[a]	Result	95% CI	P-value
Mathai, 2011[128] Adults with known or suspected PAH (N=50) Fair	Mean 61 (SD 11)	Median followup 15.7 mo	FAC (RVFAC)	Mortality	50	0.99	0.95 to 1.03	0.47
			Peak TRV	Mortality	50	0.58	0.31 to 1.10	0.10
			Pericardial effusion	Mortality	50	1.11	0.75 to 1.64	0.59
			RA size (RA area indexed)	Mortality	50	1.11	1.02 to 1.19	0.01
			TAPSE	Mortality	50	0.87	0.78 to 0.96	<0.01
Nagaya, 2000[135] Patients with PPH (N=60) Good	Mean 38 (Range 15 to 69)	Mean followup 24 ± 2 mo	BNP	Mortality	60	6.983	1.923 to 23.357	0.0031
			BNP (log)	Mortality	53	29.310	5.294 to 162.275	0.0001
			ANP (log)	Mortality	53	19.676	3.834 to 100.978	0.0004
			ANP	Mortality	60	4.641	1.347 to 15.986	0.0150
Nickel, 2008[140] Adults with IPAH (N=76) Fair	Mean 52 (Range 44 to 63)	Median followup 48 mo	BNP (ln)	Composite outcome (death or lung transplant)	76	2.62	1.78 to 3.86	<0.001
			Uric acid	Composite outcome (death or lung transplant)	76	1.56	1.27 to 1.96	<0.001
Nickel, 2012[162] Adults with IPAH (N=109) Fair	Median 55 (IQR 42 to 68)	Median 38 mo	BNP	Mortality	84	1.3	1.1 to 1.6	0.04
			Uric acid	Mortality	104	1.1	1.0 to 1.6	0.01

Table 17. Hazard ratio table for KQ 2 (continued)

Study Population (N) Quality	Age (Variability)	Duration of Followup	Index Test	Comparator	N[a]	Result	95% CI	P-value
Raymond, 2002[143] Adults with PPH (N=81) Fair	Mean 40 (SD 15)	Mean followup 36.9 ± 15.4 mo	FAC	Composite outcome (death or lung transplant)	81	0.86	0.57 to 1.28	0.454
			FAC	Mortality	81	0.70	0.39 to 1.25	0.225
			Peak TRV	Composite outcome (death or lung transplant)	81	1.00	0.77 to 1.30	0.981
			Peak TRV	Mortality	81	0.90	0.62 to 1.31	0.591
			Pericardial effusion	Composite outcome (death or lung transplant)	81	2.08	1.12 to 3.86	0.017
			Pericardial effusion	Mortality	81	3.89	1.49 to 10.14	0.003
			RA size (RA area indexed)	Composite outcome (death or lung transplant)	81	1.33	1.06 to 1.66	0.012
			RA size (RA area indexed)	Mortality	81	1.54	1.13 to 2.10	0.005
			RV size (RVED area index)	Composite outcome (death or lung transplant)	81	1.26	0.95 to 1.66	0.110
			RV size (RVED area index)	Mortality	81	1.34	0.90 to 1.98	0.148
Rhodes, 2011[144] Adults with IPAH (N=139) Good	Mean 47.6 (SD 15.8)	2 yr	BNP (square root)	Mortality	139	1.038	1.018 to 1.058	<0.001

Table 17. Hazard ratio table for KQ 2 (continued)

Study Population (N) Quality	Age (Variability)	Duration of Followup	Index Test	Comparator	N[a]	Result	95% CI	P-value
Sadushi-Kolici, 2012[160] Adults with PH (N=111) Fair	Mean 52 (SD 17)	9 yrs	Pericardial effusion	Mortality	105	6.361		0.003
Takeda, 2010[149] Adults with PAH (N=37) Good	Mean 49 (SD 18)	635 ± 510 days	BNP (log)	Mortality	37	2.79	1.55 to 5.04	0.001
Torbicki, 2003[150] Adults with PAH (N=56) Good	Mean 41 (SD 15)	Mean followup 17 ± 8.5 mo	FAC	Mortality	56	0.999	0.94 to 1.06	0.96
			BNP >median (1647 pg/mL)	Mortality	56	1.84	0.89 to 5.45	0.32
			Pericardial effusion	Mortality	56	2.77	0.89 to 8.59	0.08
			RA size (RA area)	Mortality	56	1.03	0.97 to 1.09	0.39
			cTnT (detectable)	Mortality	56	5.47	1.62 to 18.46	0.003
Utsunomiya, 2011[151] Adults with chronic PH (N=50) Good	Mean 46 (SD 13)		BNP	Mortality	50			0.006
			RA size (RA end systolic area indexed)	Mortality	50			0.005
			RIMP/MPI/ Tei index	Mortality	50			0.005
Williams, 2006[68] Adults with systemic sclerosis (N=109) Fair	Mean 60 (SD 10)	1 yr	BNP (10-fold increase FROM baseline)	Mortality	68	3.82	1.46 to 9.96	0.006
			BNP (10-fold increase IN baseline)	Mortality	68	4.82	1.29 to 18.05	0.002
Yamada, 2012[161] Patients with IPAH (N=41) Good	Mean 39 (SD 14)	45 ± 25 mo	BNP	Mortality	41	1.00	1.00 to 1.00	0.197
			Uric acid	Mortality	41	1.38	0.95 to 2.00	0.087
			BNP	Hospitalization	41	1.00	1.00 to 1.00	0.129
			Uric acid	Hospitalization	41	1.25	0.98 to 1.59	0.075

Table 17. Hazard ratio table for KQ 2 (continued)

Study Population (N) Quality	Age (Variability)	Duration of Followup	Index Test	Comparator	N[a]	Result	95% CI	P-value
Yanagisawa, 2012[159] Adults with PAH (N=46) Good	Mean 42 (SD 14)	44 ± 26 mo	BNP	Mortality	46	1.00	0.99 to 1.00	NS
Zhao, 2012[163] Patients with IPAH (N=76) Good	Mean 37 (SD 11)	Mean 24 ± 9 mo	Uric acid	Mortality	76	1.003	1.000 to 1.006	0.049

ANP = A-type natriuretic peptide; BNP = B-type natriuretic peptide; CO = cardiac output; cTnT = cardiac troponin T; CVD = collagen vascular disease; FAC = fractional area change; IQR = interquartile range; mPAP = mean pulmonary artery pressure; mo = month/months; MPI = myocardial performance index; NR = not reported; PVR = pulmonary vascular resistance; RA = right atrium; RIMP = right index of myocardial performance; RV = right ventricle; SD = standard deviation; SEM = standard error of the mean; sPAP = systolic pulmonary artery pressure; TAPSE = tricuspid annular plane systolic excursion; TRV = tricuspid regurgitant jet velocity; yr = year/years

[a]Number of patients who had the index test and comparator measured.

Meta-Analysis of Hazard Ratio Studies

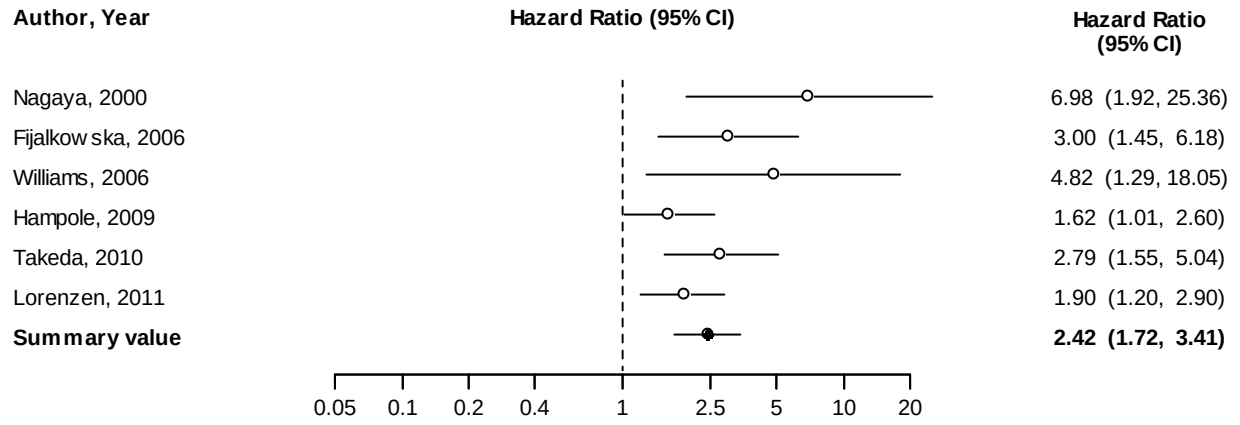
There were too few studies to permit meta-analysis assessing hazard ratios for a composite outcome. Our analysis focused on those studies that evaluated biomarkers or echocardiographic parameters as predictors of mortality. To improve the robustness of the analysis, we included only index tests that were evaluated in at least four different studies. We also concentrated on univariate hazard ratios as each study that created a multivariate model adjusted for different variables. We did not include those studies that evaluated a biomarker or echocardiographic parameter as a dichotomous outcome since these studies tended use markedly different thresholds across studies.

BNP and Mortality

Figures 16 and 17 show forest plots of the hazard ratios for BNP and mortality from 11 studies (757 patients), with values ranging from 1.62 to 6.98. Studies differed in whether and how BNP values, which tend to have a skewed distribution, were transformed for use in their analyses. Most studies used log-transformation of BNP values, while others did not describe any transformation or used a different transformation method (e.g., square root in one study). We segregated our analysis according to whether BNP values were log-transformed and found that this explained a great deal of the statistical heterogeneity of results—reducing the initial Q-value of 73.2 for 10 degrees of freedom, I^2=86.34, to Q-value of 7.78 for 5 degrees of freedom, I^2=35.72%, p=0.17, among studies using log-transformed BNP values, and Q-value of 26.10 for 4 degrees of freedom, I^2=84.68%, p<0.001, for studies using no transformation method or a different transformation method.

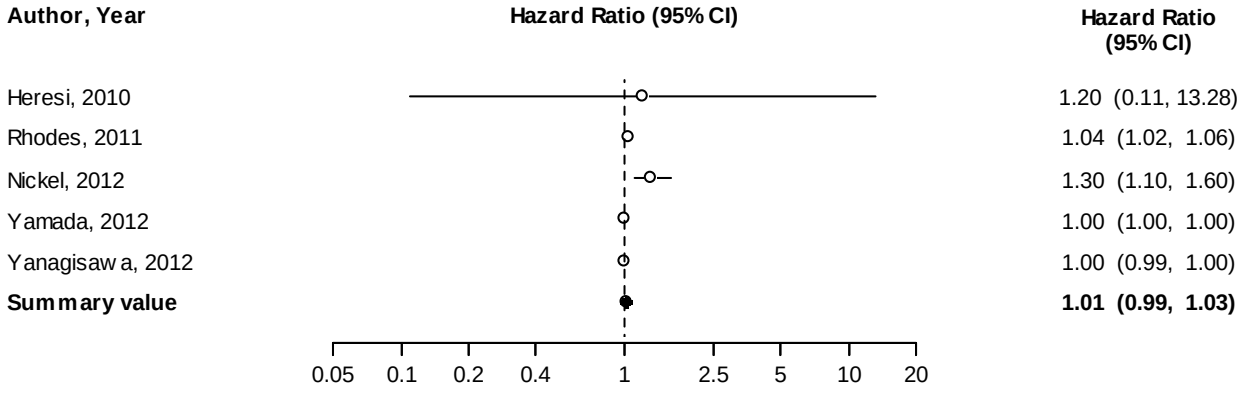
Given the reduction in heterogeneity, we analyzed those studies reporting a log-transformed value for BNP separately from the other studies. For those studies that analyzed log-transformed values for BNP, the summary hazard ratio was 2.42 (95% CI, 1.72 to 3.41), indicating that higher levels of BNP are associated with higher mortality (Figure 16). Studies differed in study population, with some looking at populations with a specific etiology for PAH[68,125] and others looking at mixed populations.[102,114,135,149] Studies evaluated either BNP[135,149] or NT-proBNP.[68,102,114,125] For those studies in which BNP values were not log-transformed, the summary hazard ratio was 1.01 (95% CI, 0.99 to 1.03), suggesting no association with mortality (Figure 17); however, we believe that these analyses suffer from limited statistical power to detect any effect and perhaps obscure any observed effect through rounding error (e.g., one study reported a hazard ratio of 1 with 95% CI from 1.0 to 1.0). Studies differed in study population, with some evaluating populations with a specific etiology for PAH[144,161,162] and others evaluating mixed populations.[115,159] Studies evaluated either BNP[115,159,161] or NT-proBNP.[144,162] We based our assessment primarily on the studies that used log-transformed BNP values. Overall for BNP, the strength of evidence is moderate based on most studies with low risk of bias, consistent results of a direct outcome, and imprecise estimates.

Figure 16. Forest plot of hazard ratio for log-transformed BNP and mortality



C I = confidence interval

Figure 17. Forest plot of hazard ratio for BNP (without mention of log-transformation) and mortality

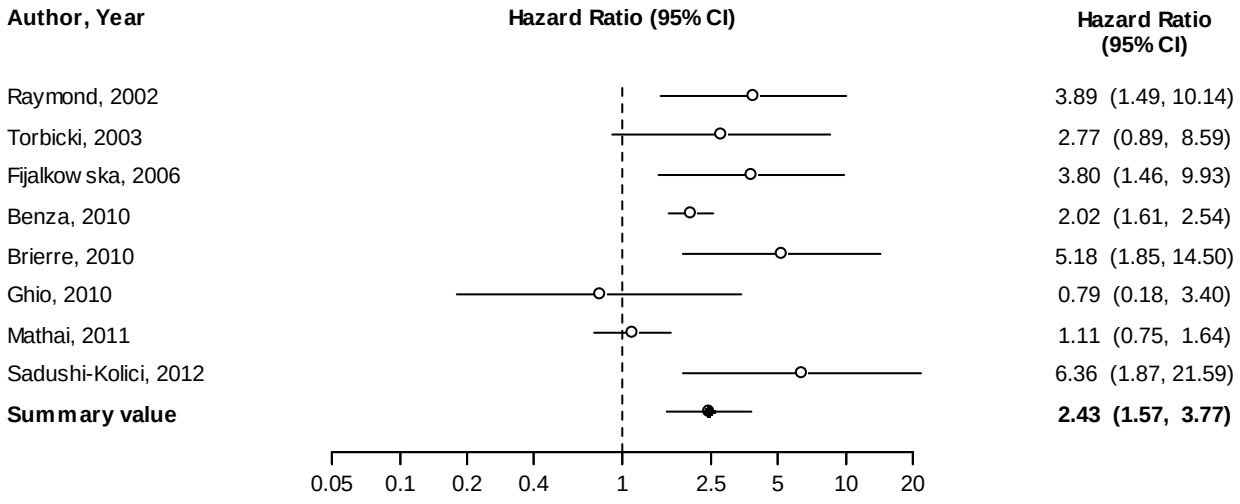


CI = confidence interval

Pericardial Effusion and Mortality

Figure 18 shows the forest plot of the hazard ratio for presence of pericardial effusion and mortality from 8 studies (2590 patients) with values ranging from 0.79 to 6.36. The summary hazard ratio was 2.43 (95% CI, 1.57 to 3.77), indicating that the presence of pericardial effusion is associated with higher mortality. There was moderate heterogeneity, with a Q-value of 20.79 for 7 degrees of freedom, I^2=66.32%, p<0.001. The two studies that reported an effect estimate smaller than the summary estimate[108,128] reported the pericardial effusion value as a combined value incorporating both presence and grade or severity. The other six studies reported only presence of effusion. The strength of evidence is rated moderate based on five studies with low risk of bias and three with moderate risk of bias, inconsistent results of a direct outcome, and imprecise estimates.

Figure 18. Forest plot of hazard ratio for pericardial effusion and mortality

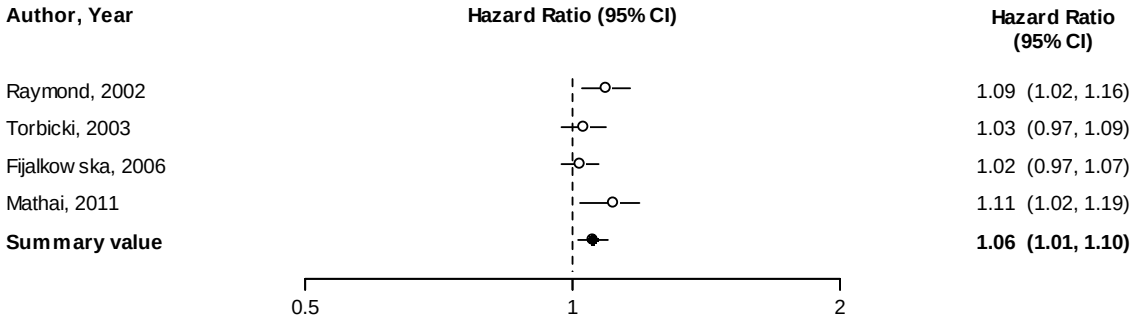


CI = confidence interval

RA Size and Mortality

Figure 19 shows the forest plot of the hazard ratio for RA size and mortality from 4 studies (242 patients) with values ranging from 1.02 to 1.11 per 1 cm^2 increment in RA size or per 1 cm^2/m increment in RA index. The summary hazard ratio was 1.06 (95% CI, 1.01 to 1.10), indicating that increased RA size is associated with increased mortality. There was moderate heterogeneity, with a Q-value of 5.04 for 3 degrees of freedom, I^2=40.51%, p=0.17. Some of the heterogeneity may be explained by the fact that both the Raymond study[143] and the Mathai study[128] reported RA area indexed to patient height while the others did not. We could find no other significant differences in the studies to explain the heterogeneity. The strength of evidence is rated moderate based on two studies with low risk of bias and two with moderate risk of bias, consistent results of a direct outcome, and precise estimates.

Figure 19. Forest plot of hazard ratio for RA size and mortality

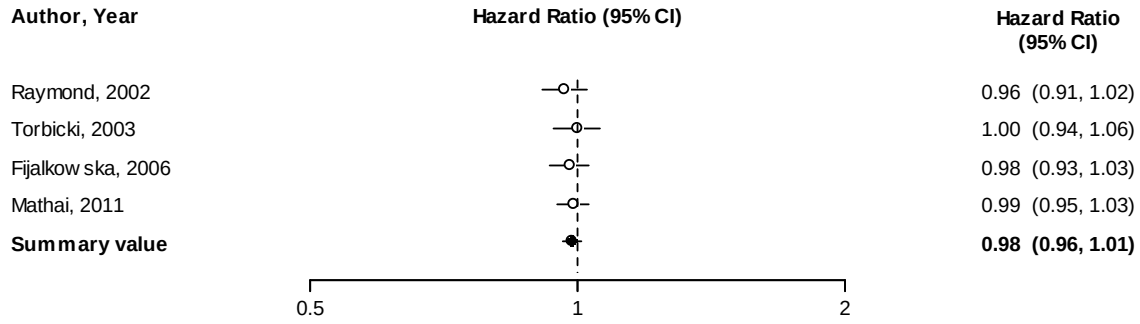


CI = confidence interval

FAC and Mortality

Figure 20 shows the forest plot of the hazard ratio for FAC and mortality from 4 studies (242 patients) with values ranging from 0.96 to 1.0 per 0.01 (1%) increment in FAC. The summary hazard ratio was 0.98 (95% CI, 0.96 to 1.01), indicating that differences in FAC had no relationship to mortality. There was low heterogeneity, with a Q-value of 0.79 for 3 degrees of freedom, I^2=0, p= 0.85. The strength of evidence is rated moderate based on two studies with low risk of bias and two with moderate risk of bias, consistent results of a direct outcome, and precise estimates.

Figure 20. Forest plot of hazard ratio for FAC and mortality

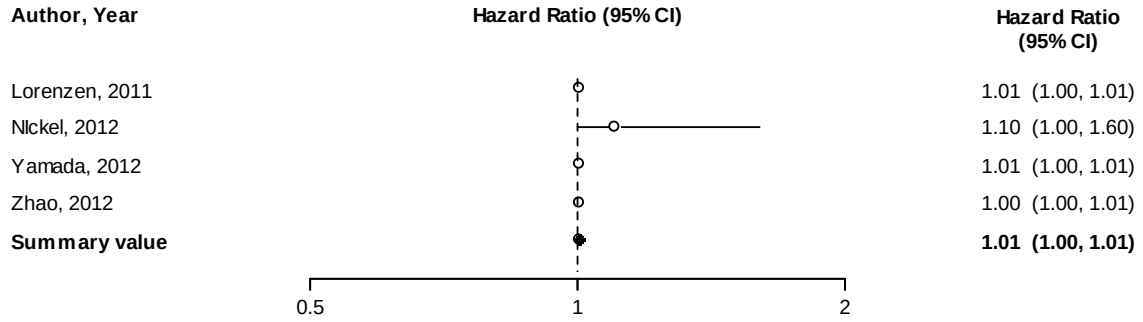


CI = confidence interval

Uric Acid and Mortality

Figure 21 shows the forest plot of the hazard ratio for uric acid and mortality from 4 studies (246 patients) with values ranging from 1.00 to 1.10 per 1 µmol/L increment in serum uric acid level. The summary hazard ratio was 1.01 (95% CI, 1.00 to 1.01), suggesting that differences in serum uric acid level had a small but detectable effect on risk of mortality. There was moderate heterogeneity, with a Q-value of 11.65 for 3 degrees of freedom, I^2=74.25%, p=0.01. Heterogeneity in these studies may have been introduced by different scales of measurements across studies and different populations. Lorenzen et al.[125] reported a statistically significant hazard ratio of 1.9 (CI, 1.5 to 2.6) for a 100 µmol/L increment in serum uric acid level; however, other studies reported hazard ratios calculated for 1 µmol/L or 1 mg/dL increments, and rounding error in the estimates precluded adjustment to a larger (clinically important) increment. Three studies[161-163] evaluated patients with IPAH, while the Lorenzen study evaluated patients with PAH from multiple etiologies.[125] The strength of evidence is rated low based on three studies with low risk of bias and one with moderate risk of bias, inconsistent results of a direct outcome, and imprecise estimates.

Figure 21. Forest plot of hazard ratio for serum uric acid level and mortality

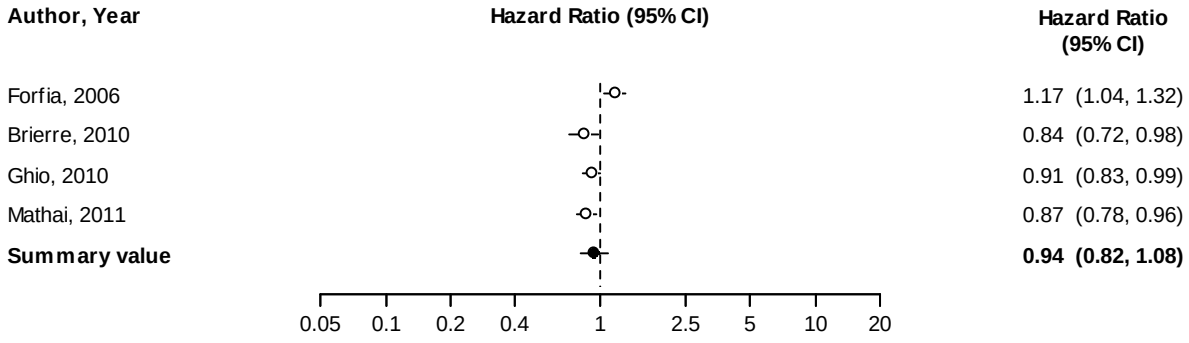


CI = confidence interval

TAPSE and Mortality

Figure 22 shows the forest plot of the hazard ratio for TAPSE and mortality from 4 studies (251 patients) with values ranging from 0.84 to 1.17. The summary hazard ratio was 0.94 (95% CI, 0.82 to 1.08), indicating that differences in TAPSE had no significant relationship to mortality. There was moderate heterogeneity, with a Q-value of 17.9 for 3 degrees of freedom, I^2=83.24%, p<0.001. Heterogeneity in these studies may have been introduced by different scales of measurements across studies and different populations. The strength of evidence is rated insufficient based on three studies with low risk of bias and one with moderate risk of bias, inconsistent results of a direct outcome, and precise estimates.

Figure 22. Forest plot of hazard ratio for TAPSE and mortality



CI = confidence interval

Evaluation of Responsiveness of Biomarkers and Echocardiography as Assessed by Changes in Mean or Median Levels

In our review, we focused only on those studies that measured mean or median values for biomarkers or echocardiographic parameters at two or more different time points or reported as a change from baseline, in order to evaluate whether changes in these measures could serve as a potential surrogate marker for response to therapy. Tables 17–19 show means, medians, and changes in either mean or median from baseline.

- Twenty-three studies including 1051 patients evaluated changes in mean values in response to therapy for a subset of 913 patients evaluating BNP (13 studies), sPAP (5), RV size (5), RIMP/MPI/Tei index (3), TRV (3), TAPSE (1), FAC (1), mPAP (1), nitric oxide (1), endothelin-1 (1) and RA size (1).

- Four studies with a total of 37 patients evaluated changes in median in response to therapy evaluating BNP (4 studies), Endothelin-1 (1), RIMP/MPI/Tei index (1), sPAP (1), FAC (1), RVEF (1).
- Eight studies with a total 935 patients evaluated mean or median change from baseline in response to therapy for a subset of 610 patients evaluating BNP (5 studies), mPAP (3), RV size (2), FAC (1), TRV (1), RIMP/MPI/Tei index (1), RA size (1) and cardiac index (1).
- Response to therapy was evaluated for the following drugs: ambrisentan (6 studies), bosentan (11), epoprostenol (10), iloprost (2), sildenafil (1), tadalafil (2), and treprostinil (3).

Due to the small number and heterogeneity of these studies in regard to index test and type of therapy, we were unable to perform meta-analysis on these data. While a few studies found changes in biomarkers or echocardiographic parameters in response to various treatments, there were insufficient data to quantitatively assess overall response or to recommend use of these markers as surrogate outcomes measures. Many of these studies also evaluated changes in patient outcomes in response to therapy, but there were no data to correlate change in biomarkers or echocardiographic parameters with these changes in outcomes.

Of the 13 studies that assessed mean values of BNP in response to various therapies (prostanoids, sildenafil, endothelin receptor antagonists, or "standard therapy"), most showed a decrease in BNP levels by approximately half after 3 to 6 months of therapy (Table 18).[93,96,106,119,124,130,133,136,167,168] Studies with longer followup times showed that the lower BNP levels remained stable throughout the course of followup.[93,119,136] One study with mean followup of 9 months showed no change in BNP levels in response to tadalafil.[172] Another study actually showed an increase in BNP levels after a mean followup duration of 20 months when patients were transitioned from bosentan to ambrisentan but a decrease in levels when ambrisentan was started as the first line endothelin receptor antagonist therapy.[173]

Four of five studies assessing changes in mean sPAP showed decreased values in response to tadalafil after 1 month of followup,[88] bosentan after 9 months of followup,[165] or epoprostenol after 6 to 24 months of followup.[137,146] One study showed no change in mean sPAP levels for unspecified monotherapy after 18 month followup or combination therapy after 12 months of followup.[121]

In three studies, mean RIMP/MPI/Tei index did not change appreciably over time following treatment with bosentan/iloprost[101] or epoprostenol[137,146] after 5 to 23 months of followup. Five studies showed no change in mean RV size after treatment with epoprostenol for 15 to 23 months of followup,[93,137] bosentan for 24 months of followup,[165] iloprost after 18 months of followup,[169] or tadalafil after 9 months of followup.[172] Mean TRV decreased slightly in one study after 22 months of treatment with epoprostenol.[137] Two studies showed no change in mean TRV over 6 months of treatment with either bosentan or ambrisentan[133] or 9 months of treatment with tadalafil.[172] There was a slight decrease in mean TAPSE value following 15 months of epoprostenol therapy in one study.[93] Studies showed no change in mean levels of endothelin-1 in response to epoprostenol after 3 months,[123] FAC in response to epoprostenol after 15 months,[93] or RA size after epoprostenol or bosentan for 24 months.[138,165] In one study, mean nitric oxide level decreased significantly over 1 year of treatment with bosentan.[92]

Table 18. Studies reporting changes in mean values over time

Study Population (N) Quality	Age (Variability)	Timing	Index Test	N	Mean	Variability	Clinical Scenario
Bharani, 2007[88] Adults and children with suspected or symptomatic PAH (N=8) Fair	Mean 28 (SD 9.38)	Baseline	sPAP	8	114.12	SD 23.14	Response to tadalafil
		1 mo	sPAP	8	88.75	SD 23.26	Response to tadalafil
Campana, 2004[93] Adults with precapillary PH (N=22) Good	Mean 50 (SD 11)	Baseline	FAC	22	0.26	SD 0.10	Response to epoprostenol
		Mean followup 15 ± 4 mo	FAC	22	0.23	SD 0.08 p=0.8	Response to epoprostenol
		Baseline	BNP	22	246	SD 162	Response to epoprostenol
		Mean followup 15 ± 4 mo	BNP	22	256	SD 180 p=0.9	Response to epoprostenol
		Baseline	RV size (RV end diastolic diameter)	22	36	SD 7.5	Response to epoprostenol
		Mean followup 15 ± 4 mo	RV size (RV end diastolic diameter)	22	39	SD 7.3 p=0.09	Response to epoprostenol
		Baseline	TAPSE	22	17.3	SD 4.4	Response to epoprostenol
		Mean followup 15 ± 4 mo	TAPSE	22	15.2	SD 4.4 p=0.04	Response to epoprostenol
Cella, 2009[92] Adults with PAH associated with CTD (N=18) Good	Mean 53.8 (SD 13.1)	Baseline	Nitric oxide	18	24.05	SD 6.04	Response to bosentan
		1 yr	Nitric oxide	18	13.92	SD 3.40 p<0.001	Response to bosentan
D'Alto, 2010[96] Adults with PAH due to CHD (N=32) Fair	Mean 37.1 (SD 13.7)	Baseline	BNP	32	760	SD 943	Response to bosentan + sildenafil
		6 mo	BNP	32	303	SD 366 p=0.008	Response to bosentan + sildenafil

Table 18. Studies reporting changes in mean values over time (continued)

Study Population (N) Quality	Age (Variability)	Timing	Index Test	N	Mean	Variability	Clinical Scenario
Feliciano, 2004[101] Adults with severe PAH (N=11) Good	Mean 42 (SD 18)	Baseline	RIMP/MPI/Tei index	11	0.8	SD 0.6	Bosentan or iloprost
		11.3 ± 7.9 mo	RIMP/MPI/Tei index	11	0.7	SD 0.4 p=0.02 (compared with baseline)	Bosentan or iloprost
Galie, 2008[106] Adults with PAH (N=201) Good	NR	Baseline	BNP	394	122.92	95% CI 93.30 to 160.82	Response to ambrisentan 5mg (Aries I)
		12 wk	BNP	394	85.75	95% CI 66.01 to 111.23	Response to ambrisentan 5mg (Aries I)
		Baseline	BNP	394	132.07	95% CI 89.72 to 193.86	Response to ambrisentan10mg (Aries I)
		12 wk	BNP	394	72.29	95% CI 53.50 to 98.72	Response to ambrisentan10mg (Aries I)
		Baseline	BNP	394	129.94	95% CI 89.49 to 188.22	Response to ambrisentan 2.5mg (Aries II)
		12 wk	BNP	394	92.68	95% CI 69.43 to 124.84	Response to ambrisentan 2.5mg (Aries II)
		Baseline	BNP	394	89.81	95% CI 58.92 to 137.58	Response to ambrisentan 5mg (Aries II)
		12 wk	BNP	394	62.74	95% CI 42.36 to 93.63	Response to ambrisentan 5mg (Aries II)
Jacobs, 2009[119] Adults with idiopathic PAH (N=16) Fair	Mean 37.0 (SD 2.8)	Baseline	BNP	11	2830	SEM 818	Response to prostanoids
		Mean followup 37.0 ± 4.4 mo	BNP	11	1574	SEM 447 p=0.049	Response to prostanoids

Table 18. Studies reporting changes in mean values over time (continued)

Study Population (N) Quality	Age (Variability)	Timing	Index Test	N	Mean	Variability	Clinical Scenario
Kaya, 2012[165] Patients with Eisenmenger syndrome (N=23) Good	Mean 31 (SD 12)	Baseline	RV size	23	35.3	SD 10.5	Response to bosentan
		Mean followup 24 ± 9 mo	RV size	23	31.8	SD 10.3 p=0.066	Response to bosentan
		Baseline	RA size	23	40.5	SD 4.5	Response to bosentan
		Mean followup 24 ± 9 mo	RA size	23	35.4	5.2 p=0.14	Response to bosentan
		Baseline	sPAP	23	118	SD 22	Response to bosentan
		Mean followup 24 ± 9 mo	sPAP	23	111	SD 19 p=0.044	Response to bosentan
		Baseline	s-prime	23	6.7	SD 1.5	Response to bosentan
		Mean followup 24 ± 9 mo	s-prime	23	8.8	SD 1.7 p=0.003	Response to bosentan
Keogh, 2011[121] Adults with PAH (N=112) Fair	Mean 51.4 (SD 17.8)	Baseline (at start of monotherapy)	sPAP	101	83	SD 23	Response to monotherapy
		Mean followup 18.7 ± 13.4 mo on monotherapy	sPAP	103	86	SD 25	Response to monotherapy
		1 yr after starting combination therapy	sPAP	112	77	SD 22	Response to combo therapy
Knirsch, 2011[129] Children with heart disease (N=103) Good	Mean 6.4 (SD 5.2)	Baseline	BNP	4	980.5	SD 994.9	Before treatment in patients with IPAH
		Baseline	BNP	6	665.2	SD 1371	Before treatment in patients with PAH 2/2 CHD
		No followup time specified	BNP	8	25.6	SD 13.2 p<0.05	Response to standardized protocol in patients with IPAH
		No followup time specified	BNP	15	152.9	SD 224.4 p<0.05	Response to standardized protocol in patients with PAH 2/2 CHD

Table 18. Studies reporting changes in mean values over time (continued)

Study Population (N) Quality	Age (Variability)	Timing	Index Test	N	Mean	Variability	Clinical Scenario
Langleben, 1999[123] Patients with PPH (N=18) Good	NR	Baseline	Endothelin-1	11	1.62	SEM 0.35	Response to epoprostenol
		3 mo	Endothelin-1	11	1.84	SEM 0.41	Response to epoprostenol
Leuchte, 2005[124] Adults with PAH (N=30) Good	Mean 46.93 (SEM 2.8)	Baseline	BNP	30	45.51	SEM 7.52	Comparison to therapy (nonspecific)
		Mean followup 12.6 ± 1.5 mo	BNP	30	58.2	SEM 11.4	Comparison to therapy (nonspecific)
Minniti, 2009[133] Adults with SCD and PH (N=14) Poor	Mean 48.9	Baseline	BNP	14	407	SD 172	Response to bosentan or ambrisentan
		2 mo	BNP	14	286	SD 63	Response to bosentan or ambrisentan
		3 mo	BNP	14	224	SD 46	Response to bosentan or ambrisentan
		Baseline	TRV	14	3.4	SD 0.1	Response to bosentan or ambrisentan
		2 mo	TRV	14	3.4	SD 0.1	Response to bosentan or ambrisentan
		3 mo	TRV	14	3.3	SD 0.1	Response to bosentan or ambrisentan
		6 mo	TRV	14	3.3	SD 0.2	Response to bosentan or ambrisentan
Morishita, 2009[138] Adults and children with PAH (N=7) Good	Median 34.6 (Range 15 to 49)	1 mo	RA size (RA area indexed)	7	18.6	SD 10.4	Response to epoprostenol
		3 mo	RA size (RA area indexed)	7	19.4	SD 10.7	Response to epoprostenol
		6 mo	RA size (RA area indexed)	7	14.6	SD 5.4	Response to epoprostenol
		1 yr	RA size (RA area indexed)	7	14.5	SD 5.8	Response to epoprostenol

Table 18. Studies reporting changes in mean values over time (continued)

Study Population (N) Quality	Age (Variability)	Timing	Index Test	N	Mean	Variability	Clinical Scenario
Nakayama, 2007[136] Patients with PPH (N=60) Good	Mean 10.7 (SD 3.5)	3 mo	BNP	27	187.0	SD 221.4	Response to epoprostenol
		1 yr	BNP	27	86.6	SD 133.9	Response to epoprostenol
		2 yr	BNP	27	85.3	SD 206.1	Response to epoprostenol
Nath, 2005[137] Adults with PPH (N=20) Good	Mean 46 (SD 11)	Baseline	RIMP/MPI/Tei index	20	0.6	SD 0.3	Response to epoprostenol
		22.7 ± 9.3 mo	RIMP/MPI/Tei index	20	0.6	SD 0.3 p=0.54	Response to epoprostenol
		Baseline	RV size	20	2.1	SD 0.9	Response to epoprostenol
		22.7 ± 9.3 mo	RV size	20	1.8	SD 1.5 p=0.07	Response to epoprostenol
		Baseline	sPAP	20	87	SD 26	Response to epoprostenol
		22.7 ± 9.3 mo	sPAP	20	75	SD 24 p=0.02	Response to epoprostenol
		Baseline	TRV	20	4.2	SD 0.6	Response to epoprostenol
		22.7 ± 9.3 mo	TRV	20	3.8	SD 0.7 p=0.02	Response to epoprostenol
Ogawa, 2012[167] Patients with pulmonary veno-occlusive disease or pulmonary capillary hemangiomatosis (N=8) Fair	Mean 26.0 (SD 3.1)	Baseline	BNP	8	381.3	SD 136.8	Response to epoprostenol
		12 mo	BNP	8	55.2	14.4 p=0.05	Response to epoprostenol

Table 18. Studies reporting changes in mean values over time (continued)

Study Population (N) Quality	Age (Variability)	Timing	Index Test	N	Mean	Variability	Clinical Scenario
Sebbag, 2001[146] Adults and children with PPH (N=16) Good	Mean 43 (SD 16)	Baseline	RIMP/MPI/Tei index	16	0.72	SD 0.22	Response to epoprostenol
		5.9 ± 4.6 mo	RIMP/MPI/Tei index	16	0.64	SD 0.17 p=0.05	Response to epoprostenol
		Baseline	sPAP	16	108	SD 19	Response to epoprostenol
		5.9 ± 4.6 mo	sPAP	16	94	SD 22 p=0.03	Response to epoprostenol
Simeoni, 2008[58] Adults with systemic sclerosis and PH (N=20) Good	Median 55 (Range 40 to 70)	Baseline	BNP	10	23.4 pmol/L	Range 11.1 to 38	Response to bosentan
		3 mo	BNP	10	26	Range 4.54 to 144 p=0.953	Response to bosentan
		7 mo	BNP	10	15.7	Range 6 to 79 p=0.600	Response to bosentan
Taguchi, 2012[168] Patients with IPAH (N=65) Good	Mean 40 (SD 13)	Baseline	BNP	65	248	SD 327	Response to combination therapy
		Mean followup 37 ± 17 mo	BNP	65	46	SD 59 p=0.085	Response to combination therapy
Takatsuki, 2012[172] Children with PAH (N=33) Good	Median 10 (Range 4 to 18)	Baseline	TRJ velocity	21	4.1	SD 0.7	Response to tadalafil
		9.0 ± 7.2 mo	TRJ velocity	21	3.9	SD 0.8 p=NS	Response to tadalafil
		Baseline	RV size	19	24.5	SD 10.1	Response to tadalafil
		9.0 ± 7.2 mo	RV size	19	23.6	SD 8.8 p=NS	Response to tadalafil
		Baseline	BNP	24	102.2	SD 283.3	Response to tadalafil
		9.0 ± 7.2 mo	BNP	24	100.2	SD 160 p=NS	Response to tadalafil

Table 18. Studies reporting changes in mean values over time (continued)

Study Population (N) Quality	Age (Variability)	Timing	Index Test	N	Mean	Variability	Clinical Scenario
Takatsuki, 2012[173] Children with PAH (N=38) Good	Median 11 (Range 2-18)	Baseline	BNP	15	49	SD 34	Response to transition to ambrisentan
		Median followup 20 mo	BNP	15	72	SD 47 p=NS	Response to transition to ambrisentan
		Baseline	BNP	23	81	SD 105	Response to the addition of ambrisentan
		Median followup 20 mo	BNP	23	53	SD 41 p=NS	Response to the addition of ambrisentan
Yang, 2012[169] Patients with Eisenmenger syndrome (N=12) Fair	Mean 33.2 (SD 12.1)	Baseline	RV size	12	53.7	SD 4.8	Response to iloprost
		Mean followup 18.6 ± 7.4 mo	RV size	12	51.4	SD 3.9 p=0.068	Response to iloprost
		Baseline	mPAP	12	62.8	SD 13.7	Response to iloprost
		Mean followup 18.6 ± 7.4 mo	mPAP	12	58.9	SD 11.7 p=0.059	Response to iloprost

ANP = A-type natriuretic peptide; BNP = B-type natriuretic peptide; CHD = congenital heart disease; CTD = connective tissue disease; CO = cardiac output; cTnT = cardiac troponin T; CVD = collagen vascular disease; FAC = fractional area change; mPAP = mean pulmonary artery pressure; mo = month/months; MPI = myocardial performance index; NR = not reported; PVR = pulmonary vascular resistance; RA = right atrium; RIMP = right index of myocardial performance; RV = right ventricle; SD = standard deviation; SEM = standard error of the mean; sPAP = systolic pulmonary artery pressure; TAPSE = tricuspid annular plane systolic excursion; TRV = tricuspid regurgitant jet velocity; wk=week/weeks; yr=year/years

The four studies that assessed change in median levels of BNP in response to therapy with bosentan showed decrease by approximately half after 3 to 12 months of therapy (Table 19).[97,120,164,166] However, one of these studies subsequently showed increasing levels of BNP after 30 months of therapy.[120] One study showed an overall moderate decrease in median RIMP/MPI/Tei index levels after 30 months of therapy but no significant change in median values of sPAP, FAC, or RVEF after 30 months of therapy.[120]

Table 19. Studies reporting changes in median levels over time

Study Population (N) Quality	Age (Variability)	Timing	Index Test	N	Median	Variability (Range)	Clinical Scenario
Dimitroulas, 2007[97] Adults with PAH associated with scleroderma (N=10) Good	Median 58 (Range 39 to 74)	Baseline	Natriuretic peptides/BNP	10	474		Response to bosentan
		20 wk	Natriuretic peptides/BNP	10	238	198-335 (p=0.002 compared with baseline)	Response to bosentan
Halank, 2011[164] Adults with portopulmonary hypertension (N=14) Fair	Median 57 (Range 46 to 63)	Baseline	NT-proBNP	11	1226 pg/mL	113 to 2521	Response to ambrisentan
		12 mo	NT-proBNP	11	224	59 to 583	Response to ambrisentan
Ho, 2009[120] Adults with PAH (N=6) Good	Mean 33 (NR)	Baseline	RIMP/MPI/Tei index	6	0.85	0.49 to 1.75	Response to bosentan
		6 mo	RIMP/MPI/Tei index	6	0.55	0.22 to 0.81	Response to bosentan
		1 yr	RIMP/MPI/Tei index	6	0.63	0.33 to 1.49	Response to bosentan
		18 mo	RIMP/MPI/Tei index	4	0.70	0.26 to 1.10	Response to bosentan
		2 yr	RIMP/MPI/Tei index	4	0.73	0.62 to 1.08	Response to bosentan
		30 mo	RIMP/MPI/Tei index	4	0.67	0.45 to 1.16	Response to bosentan
		Baseline	sPAP	6	98	50 to 163	Response to bosentan
		6 mo	sPAP	6	103	37 to 142	Response to bosentan
		1 yr	sPAP	6	92	42 to 127	Response to bosentan
		18 mo	sPAP	4	118	28 to 143	Response to bosentan
		2 yr	sPAP	4	118	61 to 136	Response to bosentan
		30 mo	sPAP	4	108	87 to 117	Response to bosentan
		Baseline	Fractional area change	6	22	13 to 28	Response to bosentan
		6 mo	Fractional area change	6	27	15 to 54	Response to bosentan

Table 19. Studies reporting changes in median levels over time (continued)

Study Population (N) Quality	Age (Variability)	Timing	Index Test	N	Median	Variability (Range)	Clinical Scenario
Ho, 2009[120] Adults with PAH (N=6) Good (continued)		1 yr	Fractional area change	6	26	9 to 49	Response to bosentan
		18 mo	Fractional area change	4	35	26 to 53	Response to bosentan
		2 yr	Fractional area change	4	27	16 to 33	Response to bosentan
		30 mo	Fractional area change	4	21	19 to 45	Response to bosentan
		Baseline	Natriuretic peptides/BNP	6	224	20 to 169	Response to bosentan
		6 mo	Natriuretic peptides/BNP	6	111	13 to 231	Response to bosentan
		1 yr	Natriuretic peptides/BNP	6	136	5 to 249	Response to bosentan
		18 mo	Natriuretic peptides/BNP	4	215	14 to 352	Response to bosentan
		2 yr	Natriuretic peptides/BNP	4	193	92 to 293	Response to bosentan
		30 mo	Natriuretic peptides/BNP	4	203	81 to 376	Response to bosentan
		Baseline	RVEF	6	30	14 to 35	Response to bosentan
		6 mo	RVEF	6	39	17 to 71	Response to bosentan
		1 yr	RVEF	6	35	15 to 60	Response to bosentan
		1 yr	RVEF	6	32	15 to 83	Response to bosentan
		18 mo	RVEF	4	45	31 to 77	Response to bosentan
		2 yr	RVEF	4	38	20 to 50	Response to bosentan
		30 mo	RVEF	4	28	24 to 62	Response to bosentan
Kopec, 2012[166] Adults with Eisenmenger syndrome (N=7) Fair	Median 40.0 (Range 30.0 to 56.0)	Baseline	Natriuretic peptides/BNP	7	260.8	190.6 to 502.9	Response to bosentan
		3 mo	Natriuretic peptides/BNP	7	169	144.9 to 341.8 p=0.02	Response to bosentan
		Baseline	Endothelin-1	7	2.5	1.7 to 2.8	Response to bosentan
		3 mo	Endothelin-1	7	4.5	2.6 to 5.3 p=0.02	Response to bosentan

BNP = B-type natriuretic peptide; mo = month/months; NR = not reported; RVEF = right ventricle ejection fraction; wk = week/weeks; yr = year/years

Seven studies assessed mean change from baseline for BNP or various echocardiographic parameters (Table 20). One study evaluated response to therapy with epoprostenol over 3 months and showed mild increase in RV size, decrease in FAC, and minimal decrease in TR jet velocity.[116] Another study evaluated response to 4 months of therapy with bosentan or sildenafil and showed—in response to bosentan—decrease in RV size, minimal increase in CI, minimal decrease in RIMP/MPI/Tei index, increase in RA size, decrease in BNP, and decrease in RV size, and—in response to sildenafil—greater decrease in RV size, RIMP/MPI/Tei index and BNP and decrease in RA size but similar response in CI.[156] Another study showed decrease in mean BNP levels after 6 months of therapy with ambrisentan.[171] Two studies showed decrease in median levels of BNP in response to treprostinil after 6 weeks with some attenuation of response after 3 months[131] and after 6 months of therapy with ambrisentan.[131] Three studies showed a decrease from baseline for mean levels of mPAP, one after 3 months therapy with bosentan,[94] one after 3 months therapy with epoprostenol[85] and one with persistently declining levels during 3 years of therapy with ambrisentan.[174]

Table 20. Studies reporting mean or median change from baseline

Study Population (N) Quality	Age (Variability)	Timing	Result	Index Test	N	Results	Variability	Clinical Scenario
Badesch, 2012[171] Adults with PAH (N=224) Good	Mean 55 (SD 16)	Baseline	Mean	Natriuretic peptides/ BNP	224	335	SD 413	Response to ambrisentan
		6 mo	Mean change	Natriuretic peptides/ BNP	224	-26	95% CI -34 to -16	Response to ambrisentan
Barst, 1996[85] Adults with PPH (N=81) Good	NR for cohort	3 mo	Mean change	mPAP	41	-4.8	SE 1.3	Response to epoprostenol
Channick, 2001[94] Adults with PPH or PAH associated with scleroderma (N=32) Good	NR for cohort	3 mo	Mean change	mPAP	20	-1.6	SE 1.2	Response to bosentan
Hinderliter, 1997[116] Adults with PPH (N=81) Fair	NR for cohort	Baseline	Mean	RV size	38	21.2	SE 0.7	Response to epoprostenol
		Baseline	Mean	Fractional area change	38	19.2	SE 1.2	Response to epoprostenol
		Baseline	Mean	TR jet velocity	36	4.3	SE 0.1	Response to epoprostenol
		3 mo	Median change	RV size	33	0.4		Response to epoprostenol
		3 mo	Median change	Fractional area change	33	-2.2		Response to epoprostenol
		3 mo	Median change	TR jet velocity	32	-0.04		Response to epoprostenol
McLaughlin, 2010[131] Adults with PAH (N=235) Good	Mean 54 (Range 18 to 75)	6 wk	Median change	Natriuretic peptides/ BNP	86	-71	p<0.0003	Response to treprostinil
		3mo	Median change	Natriuretic peptides/ BNP	73	-57	IQR -396.0 to 34.0	Response to treprostinil

Table 20. Studies reporting mean or median change from baseline (continued)

Study Population (N) Quality	Age (Variability)	Timing	Result	Index Test	N	Results	Variability	Clinical Scenario
Wilkins, 2005[156] Adults with IPAH or PAH associated with CTD (N=26) Good	NR for cohort	4 mo	Mean change	RV size	12	-3	95% CI -7.5 to 1.5	Response to bosentan
		4 mo	Mean change	Cardiac Index	12	0.3	95% CI 0.1 to 0.4 p=0.01	Response to bosentan
		4 mo	Mean change	RIMP/MPI/Tei Index	12	-0.02	95% CI -0.1 to 0.11	Response to bosentan
		4 mo	Mean change	RA size	12	4	95% CI -16 to 23	Response to bosentan
		4 mo	Mean change	Natriuretic peptides/ BNP	12	-5.9	95% CI -35 to 24	Response to bosentan
		4 mo	Mean change	RV size	13	-8.8	95% CI -16 to -2 p=0.05	Response to sildenafil
		4 mo	Mean change	Cardiac Index	13	0.3	95% CI 0.1 to 0.4 p=0.01	Response to sildenafil
		4 mo	Mean change	RIMP/MPI/Tei Index	13	-0.11	95% CI -0.23 to 0.01	Response to sildenafil
		4 mo	Mean change	RA size	13	-4	95% CI -19 to 12	Response to sildenafil
		4 mo	Mean change	Natriuretic peptides/ BNP	13	-19.4	95% CI -34 to -5	Response to sildenafil

Table 20. Studies reporting mean or median change from baseline (continued)

Study Population (N) Quality	Age (Variability)	Timing	Result	Index Test	N	Results	Variability	Clinical Scenario
Yoshida, 2012[174] Adults with PAH (N=21) Fair	Mean 45.6 (SD 12.6)	Baseline	Mean	Natriuretic peptides/	21	191.1	SD 241.4	Response to ambrisentan
		Baseline	Mean	mPAP	20	48.1	SD 17	Response to ambrisentan
		6 mo	Mean change	Natriuretic peptides/	20	-109.5	SD 170.5	Response to ambrisentan
		6 mo	Mean change	mPAP	21	-10	SD 7.4 95% CI -13.5 to -6.4	Response to ambrisentan
		1 yr	Mean change	Natriuretic peptides/	21	-70.4	SD 211.5	Response to ambrisentan
		1 yr	Mean change	mPAP	19	-7.1	SD 10.1 95% CI -11.9 to -2.2	Response to ambrisentan
		2 yr	Mean change	Natriuretic peptides/	19	-117.1	SD 183.8	Response to ambrisentan
		2 yr	Mean change	mPAP	16	-10.9	SD 10.8 95% CI -16.6 to -5.1	Response to ambrisentan
		3 yr	Mean change	Natriuretic peptides/	6	-146.5	SD 218.6	Response to ambrisentan
		3 yr	Mean change	mPAP	6	-13.9	SD 8.9 95% CI -23.2 to -4.5	Response to ambrisentan

BNP = B-type natriuretic peptide; CI = confidence interval; IQR = interquartile range; mPAP = mean pulmonary artery pressure; mo = month/months; MPI = myocardial performance index; NR = not reported; PVR = pulmonary vascular resistance; RA = right atrium; RIMP = right index of myocardial performance; RV = right ventricle; RVEF = right ventricle ejection fraction; SD = standard deviation; SEM = standard error of the mean; sPAP = systolic pulmonary artery pressure; TAPSE = tricuspid annular plane systolic excursion; TRV = tricuspid regurgitant jet velocity; wk = week/weeks; yr = year/years

Summary Strength of Evidence for KQ 2

The strength of evidence ratings for the most commonly reported biomarkers and echocardiographic parameters are summarized in Table 21 (assessment of prognostic value) and Table 22 (assessment of predictive value).

Table 21. Summary strength of evidence for KQ 2: assessment of prognostic value

Comparison	Number of Studies (Patients)	Domains				Strength of Evidence Correlation Coefficient (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
BNP compared with RHC-mPAP	14 (606)	Low (12) Moderate (1) High (1)	Consistent	Indirect	Precise	**SOE = Moderate** 0.39 (0.31 to 0.47) Serum BNP level shows moderate correlation with mPAP
BNP compared with RHC-PVR	13 (684)	Low (11) Moderate (1) High (1)	Inconsistent	Indirect	Precise	**SOE = Low** 0.46 (0.31 to 0.59) Serum BNP level shows moderate correlation with PVR
BNP compared with RHC-RAP	12 (645)	Low (11) Moderate (1)	Consistent	Indirect	Precise	**SOE = Moderate** 0.47 (0.40 to 0.54) Serum BNP level shows moderate correlation with RAP
BNP compared with RHC-CI	10 (550)	Low (9) Moderate (1)	Inconsistent	Indirect	Precise	**SOE = Low** -0.42 (-0.54 to -0,28) Serum BNP level shows negative moderate correlation with cardiac index
BNP compared with RHC-PCWP	5 (319)	Low (4) High (1)	Consistent	Indirect	Imprecise	**SOE = Low** 0.16 (0.01 to 0.31) Serum BNP level shows poor correlation with PCWP
BNP compared with 6MWD (absolute)	9 (484)	Low (8) High (1)	Inconsistent	Direct	Precise	**SOE = Moderate** -0.46 (-0.55 to -0.35) Serum BNP level shows negative moderate correlation with 6MWD
Echocardio-graphy-derived sPAP compared with RHC-sPAP	9 (362)	Low (6) Moderate (3)	Inconsistent	Indirect	Precise	**SOE = Low** 0.76 (0.53 to 0.89) sPAP estimated by echocardiography shows good correlation with sPAP from RHC

6MWD = 6-minute walk distance; BNP = B-type natriuretic peptide; CI = confidence interval; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; RAP = right atrial pressure; RHC = right heart catheterization; SOE = strength of evidence; sPAP = systolic pulmonary artery pressure

Table 22. Summary strength of evidence for KQ 2: assessment of predictive value

Comparison	Number of Studies (Patients)	Domains				Strength of Evidence Hazard Ratio (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
BNP (log-transformed)	6 (407)	Low (5) Moderate (1)	Consistent	Direct	Imprecise	**SOE = Moderate** 2.42 (1.72 to 3.41)) Increase in log-transformed BNP level is a good predictor of mortality
Pericardial effusion	8 (2590)	Low (5) Moderate (3)	Inconsistent	Direct	Imprecise	**SOE = Moderate** 2.43 (1.57 to 3.77) Presence of pericardial effusion is a strong predictor of mortality, although there was wide variability in results for this measure
RA size	4 (242)	Low (2) Moderate (2)	Inconsistent	Direct	Precise	**SOE = Moderate** 1.06 (1.01 to 1.10) RA size is a predictor of mortality
FAC	4 (242)	Low (2) Moderate (2)	Consistent	Direct	Precise	**SOE = Moderate** 0.98 (0.96 to 1.01) FAC is a poor predictor of mortality
Uric acid	4 (246)	Low (3) Moderate (1)	Inconsistent	Direct	Imprecise	**SOE = Low** 1.01 (1.00 to 1.01) Small increase in mortality but imprecision of estimates limit these data
TAPSE	4 (251)	Low (3) Moderate (2)	Inconsistent	Direct	Imprecise	**SOE = Insufficient** Inconsistent results between studies lead to uncertainty

BNP = B-type natriuretic peptide; CI = confidence interval; FAC = fractional area change; RA = right atrium; RAP = right atrial pressure; SOE=strength of evidence

KQ 3: Pharmacotherapy for PAH

For patients with PAH, what are the comparative effectiveness and safety of monotherapy or combination therapy for PAH using calcium channel blockers, prostanoids, endothelin antagonists, or phosphodiesterase inhibitors on intermediate-term and long-term patient outcomes?

Key Points

- In patients who have been receiving monotherapy, combination therapy appears to be moderately more effective than continuation of monotherapy for improving 6-minute walk distance (6MWD), with a magnitude of effect that is approximately equal to the estimated minimal important difference (MID) of 6MWD for PAH of 33 meters (low strength of evidence).
- We did not identify any eligible studies that evaluated the comparative effectiveness of calcium channel blockers on intermediate-term and long-term patient outcomes, or that randomized treatment- naïve patients to monotherapy versus combination therapy, or that directly compared two drug classes.
- Although we did not intend to exclude studies of children, the inclusion criterion requiring reporting intermediate-term and long-term patient outcomes had the effect of eliminating randomized clinical trials of children with PAH.
- Prostanoids were associated with lower mortality when compared with standard therapy or placebo (low strength of evidence). Current evidence is inconclusive regarding a reduction in mortality associated with treatment with endothelin antagonists or phosphodiesterase inhibitors (insufficient strength of evidence).
- Endothelin antagonists, phosphodiesterase inhibitors, and prostanoids were all associated with improved 6MWD after 8 to 16 weeks of therapy with a magnitude of effect that is approximately equal to the estimated minimal important difference (MID) of 6MWD for PAH of 33 meters (moderate strength of evidence).
- Endothelin antagonists and phosphodiesterase inhibitors were associated with lower incidence of hospitalization when compared with standard therapy or placebo (moderate strength of evidence). Current evidence is inconclusive regarding a reduction in hospitalization associated with treatment with prostanoids (insufficient strength of evidence).
- Endothelin antagonists, phosphodiesterase inhibitors, and prostanoids were associated with statistically significant improvements in most or all hemodynamic measures such as PVR, mPAP, and cardiac index (low strength of evidence) compared with placebo or standard therapy. The clinical significance of the magnitude of the observed changes in these intermediate outcomes is unclear.
- Among commonly reported adverse events, there was a higher incidence of jaw pain associated with aerosolized prostanoid treatment compared with placebo (high strength of evidence) and cough associated with aerosolized prostanoids versus placebo (high strength of evidence). In addition, headache was associated with phosphodiesterase inhibitors compared with placebo or standard therapy (moderate strength of evidence), and flushing was associated with phosphodiesterase inhibitors (moderate strength of

evidence) and aerosolized prostanoids (moderate strength of evidence) compared with placebo or standard therapy.

Description of Included Studies

We identified 37 unique studies involving a total of 4192 patients that evaluated the comparative effectiveness and safety of monotherapy or combination therapy for PAH. Of these studies, 28 were RCTs and 9 were nonrandomized comparative observational studies. We describe the findings from these studies separately by study design below.

Study Characteristics

Randomized Controlled Trials

Twenty-eight RCTs involving a total of 3613 patients evaluated the comparative effectiveness and safety of monotherapy or combination therapy for PAH.[85,88,94,106,131,156,181-200] Of these, 28 RCTs, 18 (64%) were rated good quality, 9 (32%) fair quality, and 1 (4%) was poor quality. Nineteen studies (68%) were funded by industry, one by private foundation, one by government and private funding, one by private and industry funding, one by industry and "other" funding, and five did not clearly report funding sources.

Study characteristics for each of the 28 RCTs relevant to KQ 3 are presented in Table 23. Studies are organized alphabetically by drug and include patient population, size, and quality; study arms and size; trial duration and followup; and outcome measures. The mean patient ages ranged from 28 to 50 years old. Twenty studies enrolled patients with PAH,[85,88,106,131,156,181,182,184,186-189,192,193,196-200] four studies enrolled patients with PAH associated with systemic sclerosis (formerly scleroderma),[94,185,194] and two studies enrolled patients with Eisenmenger syndrome.[183,195] Two studies enrolled a minority of patients with PH other than PAH: one included patients with chronic thromboembolic PH (28%);[190] and another included patients with PH owing either to lung disease or chronic thromboembolic PH (37%).[191]

Twenty-one studies compared a single drug (monotherapy) with placebo or standard therapy and included the following drugs: bosentan (6 studies), sildenafil (2), iloprost (2), epoprostenol (3), tadalafil (3), ambrisentan (2), treprostinil (3), and vardenafil (1). For the purposes of this analysis, the standard therapy arms were grouped with the placebo arms. Standard therapies included supportive therapy (diuretics, oxygen, digoxin, oral anticoagulants) with or without calcium channel blockers, but not including newer specific vasodilator medications. One study was a head-to-head comparison of bosentan and sildenafil. The remaining five studies randomized patients who had previously received monotherapy to either continued monotherapy with that drug or continued therapy with that drug plus the addition of a second drug. For the purpose of this report, we consider these studies to represent a comparison of combination therapy with monotherapy—with the understanding that this study design does not address the question of whether initiating two drugs is superior to initiating a single drug to treatment-naïve patients.

The remaining five studies compared combination therapy with monotherapy: intravenous (IV) epoprostenol plus bosentan versus IV epoprostenol plus placebo, sildenafil plus IV epoprostenol versus IV epoprostenol plus placebo, bosentan plus aerosolized iloprost versus bosentan, bosentan plus aerosolized iloprost versus bosentan plus placebo, and aerosolized treprostinil plus bosentan or sildenafil versus bosentan or sildenafil plus placebo. We did not

identify any eligible studies published after 1990 that evaluated the safety or efficacy of calcium channel blockers on intermediate-term or long-term patient outcomes.

Most studies (85%) were multicenter trials; three were single-center trials, and four did not report the number of centers. Study locations included Europe (19 studies), United States (15), Asia (8), Canada (6), Australia or New Zealand (6), United Kingdom (4), South America (4), Israel (3), Mexico (3), Central America (2), Africa (1), and unreported or unclear setting (6).

The studies reported the following outcomes: 6MWD (27 studies), mortality (21), dyspnea (17), RHC indices (18), functional class (13), hospitalization for worsening PAH (10), quality of life (11), lung transplantation (5), right heart failure or right ventricular dysfunction (4), and brain natriuretic peptide (4). Twenty-one studies reported harms or adverse events.

Table 23. Study characteristics table for KQ 3 (RCTs)

Study Population (N) Quality	Study Arms (N)	Trial Duration (Weeks)	Followup Assessments (Weeks)	Outcome Measures
AMBRISENTAN				
Individual Drug Studies				
Galie, 2008[106] ARIES-1 (US, Mexico, South America, Australia, and Europe) PAH (N=201) Good	• Ambrisentan 5 mg daily (N=67) • Ambrisentan 10 mg daily (N=67) • Placebo (N=67)	12	4, 8, 12, 48	• Mortality • 6MWD • Dyspnea • Functional class • Quality of life • Hospitalization • BNP • Adverse events
Galie, 2008[106] ARIES-2 (Europe, Israel, and South America) PAH (N=192) Good	• Ambrisentan 2.5 mg daily (N=64) • Ambrisentan 5 mg daily (N=63) • Placebo (N=65)	12	4, 8, 12, 48	• Mortality • 6MWD • Dyspnea • Functional class • Quality of life • Hospitalization • BNP • Adverse events
BOSENTAN				
Individual Drug Studies				
Barst, 2010[185] ASSET-1 SCD with PAH (N=14) Fair	• Bosentan 62.5 mg 2 times daily, then 125 mg 2 times daily (N=6) • Placebo (N=8)	16	16	• Mortality • 6MWD • RHC
Barst, 2010[185] ASSET-2 PH (N=12) Fair	• Bosentan 62.5 mg 2 times daily, then 125 mg 2 times daily (N=5) • Placebo (N=7)	16	16	• Mortality • 6MWD • RHC
Channick, 2001[94] PPH or PH due to SCD (N=32) Good	• Bosentan 62.5 mg 2 times daily, then 125 mg 2 times daily (N=21) • Placebo (N=11)	12	4, 8, 12, 20, 28	• 6MWD • Dyspnea • Functional class • Transplantation • RHC • Adverse events

Table 23. Study characteristics table for KQ 3 (RCTs) (continued)

Study Population (N) Quality	Study Arms (N)	Trial Duration (Weeks)	Followup Assessments (Weeks)	Outcome Measures
BOSENTAN (continued)				
Individual Drug Studies				
Galie, 2006[183] BREATHE-5 Eisenmenger syndrome (N=54) Good	• Bosentan 62.5 mg 2 times daily, then 125 mg 2 times daily (N=37) • Placebo (N=17)	4	4	• 6MWD • Functional class • RHC • Adverse events
Galie, 2008[184] EARLY PAH (N=185) Good	• Bosentan 62.5 mg 2 times daily, then 125 mg 2 times daily (N=93) • Placebo (N=92)	24	24	• Mortality[a] • 6MWD[a] • Dyspnea[a] • Functional class[a] • Quality of life[a] • Hospitalization[a] • RHC[a] • Adverse events[a]
Rubin, 2002[182] BREATHE PAH (N=213) Good	• Bosentan 62.5 mg 2 times daily, then 125 mg 2 times daily (N=74) • Bosentan 62.5 mg 2 times daily, then 250 mg 2 times daily (N=70) • Placebo (N=69)	12	4, 8, 16	• Mortality • 6MWD • Dyspnea • Functional class • Hospitalization • Echocardiography • Adverse events
Direct Drug Comparison Studies				
Wilkins, 2005[156] SERAPH PAH (N=26) Good	• Bosentan 62.5 mg 2 times daily, then 125 mg 2 times daily (N=12) • Sildenafil 50 mg 2 times daily, then 50 mg 3 times daily (N=14)	16	16	• Mortality • 6MWD • Quality of life • Right ventricular dysfunction • Echocardiography • BNP

Table 23. Study characteristics table for KQ 3 (RCTs) (continued)

Study Population (N) Quality	Study Arms (N)	Trial Duration (Weeks)	Followup Assessments (Weeks)	Outcome Measures
BOSENTAN (continued)				
Combination Drug Studies				
Humbert, 2004[186] BREATHE-2 PAH (N=33) Good	• Epoprostenol + bosentan 62.5 mg 2 times daily, then 125 mg 2 times daily (N=22) • Epoprostenol + placebo (N=11)	16	16	• 6MWD • Dyspnea • Functional class • Hospitalization • Right heart failure • RHC • Adverse events
EPOPROSTENOL				
Individual Drug Studies				
Badesch, 2000[194] PH associated with SCD spectrum of disease (N=111) Fair	• Epoprostenol ≤2 ng/kg, then adjusted (N=56) • Conventional therapy only (N=55)	12	1, 6, 12	• Mortality • 6MWD • Dyspnea • RHC • Adverse events
Barst, 1996[85] PPH (N=81) Good	• Epoprostenol 4 ng/kg, then adjusted (N=41) • Conventional therapy only (N=40)	12	1, 6, 12	• Mortality • 6MWD • Quality of life • Transplantation • RHC • Adverse events
Rubin, 1990[181] PPH (N=23) Good	• Intravenous epoprostenol 1–2 ng/kg per minute initially, then increased as tolerated (N=11) • Conventional therapy (N=12)	8	8	• Mortality • 6MWD • RHC • Adverse events

Table 23. Study characteristics table for KQ 3 (RCTs) (continued)

Study Population (N) Quality	Study Arms (N)	Trial Duration (Weeks)	Followup Assessments (Weeks)	Outcome Measures
ILOPROST				
Individual Drug Studies				
Olschewski, 2002[190] Severe PAH or chronic thromboembolic PH (N=203) Good	• Aerosolized iloprost (N=101) • Placebo (N=102)	12	4, 8, 12	• Mortality • 6MWD • Dyspnea • Functional class • Quality of life • Transplantation • Right ventricular dysfunction • RHC • Adverse events
Olschewski, 2010[191] AIR IPAH or other PH (N=63) Fair	• Aerosolized iloprost (N=30) • Conventional therapy only (N=33)	12	12, 104	• Mortality • 6MWD • Dyspnea • Functional class • Quality of life • Right heart failure • RHC • Adverse events
Combination Drug Studies				
Hoeper, 2006[192] COMBI IPAH (N=40) Fair	• Bosentan 125 mg 2 times daily + aerosolized iloprost (N=19) • Bosentan 125 mg (N=21)	12	6, 12	• 6MWD • Adverse events
McLaughlin, 2006[193] PAH (N=67) Good	• Bosentan + aerosolized iloprost (N=34) • Bosentan + placebo (N=33)	12	4, 8, 12	• 6MWD • Dyspnea • Functional class • Hospitalization • RHC • Adverse events

Table 23. Study characteristics table for KQ 3 (RCTs) (continued)

Study Population (N) Quality	Study Arms (N)	Trial Duration (Weeks)	Followup Assessments (Weeks)	Outcome Measures
SILDENAFIL				
Individual Drug Studies				
Barst, 2011[188] STARTS-1 PAH (N=234) Fair	• Low-dose sildenafil (N=42) • Medium-dose sildenafil (N=55) • High-dose sildenafil (N=77) • Placebo (N=60)	16	16, >156	• Mortality • Functional class • Quality of life • RHC • Adverse events
Galie, 2005[187] SUPER PAH (N=277) Good	• Sildenafil 20 mg 3 times daily (N=69) • Sildenafil 40 mg 3 times daily (N=67) • Sildenafil 80 mg 3 times daily (N=71) • Placebo (N=70)	12	4, 8, 12, 52, 156	• Mortality • 6MWD • Dyspnea • Hospitalization • Adverse events • RHC
Combination Drug Studies				
Simonneau, 2008[189] PACES PAH (N=267) Good	• Sildenafil 20 mg 3 times daily + epoprostenol, then up to 80 mg 3 times daily + epoprostenol (N=134) • Placebo + epoprostenol (N=133)	16	4, 8, 12, 16	• Mortality • Dyspnea • Quality of life • Hospitalization • Transplantation • Adverse events
TADALAFIL				
Individual Drug Studies				
Bharani, 2007[88] PAH (N=11) Fair	• Tadalafil 20 mg daily (N=11) • Placebo 20 mg daily (N=11)	4	4	• 6MWD[a] • Dyspnea[a] • Functional class[a] • Echocardiography[a]
Galie, 2009[196] PHIRST PAH (N=405) Good	• Tadalafil 2.5 mg daily (N=82) • Tadalafil 10 mg daily (N=82) • Tadalafil 20 mg daily (N=80) • Tadalafil 40 mg daily (N=79) • Placebo (N=82)[b]	16	4, 8, 12, 16	• Mortality • 6MWD • Functional class • Hospitalization • RHC • Adverse events

Table 23. Study characteristics table for KQ 3 (RCTs) (continued)

Study Population (N) Quality	Study Arms (N)	Trial Duration (Weeks)	Followup Assessments (Weeks)	Outcome Measures
TADALAFIL (continued)				
Individual Drug Studies (continued)				
Mukhopadhyay, 2011[195] Eisenmenger syndrome (N=28) Fair	• Tadalafil 40 mg daily (N=28) • Placebo (N=28)	6	6	• 6MWD[a] • RHC[a]
TREPROSTINIL				
Individual Drug Studies				
Hiremath, 2010[199] TRUST PAH (N=44) Fair	• Intravenous treprostinil 4 ng/kg/min, then adjusted (N=30) • Placebo (N=14)	12	12	• Mortality • 6MWD • Dyspnea • Functional class • Adverse events
McLaughlin, 2003[198] PPH (N=26) Poor	• Subcutaneous treprostinil 2.5-5.0 ng/kg/min, then adjusted (N=17) • Placebo (N=9)	8	8	• 6MWD[a] • Dyspnea[a] • Adverse events[a]
Simonneau, 2002[197] PAH (N=470) Good	• Subcutaneous treprostinil 1.25 ng/kg/min, then adjusted (N=233) • Placebo (N=236)	12	12	• Mortality • 6MWD • Dyspnea • Quality of life • Transplantation • Adverse events

Table 23. Study characteristics table for KQ 3 (RCTs) (continued)

Study Population (N) Quality	Study Arms (N)	Trial Duration (Weeks)	Followup Assessments (Weeks)	Outcome Measures
TREPROSTINIL (continued)				
Combination Drug Studies				
McLaughlin, 2010[131] TRIUMPH 1 Severe PAH (N=235) Good	• Aerosolized treprostinil 18 mcg 4 times daily, gradually increased to 54 mcg+ bosentan/ sildenafil (N=115) • Placebo + bosentan/sildenafil (N=120)	12	6, 12	• Mortality • 6MWD • Dyspnea • Functional class • Quality of life • Hospitalization • Transplantation • BNP • Adverse events
VARDENAFIL				
Individual Drug Studies				
Jing, 2011[200] EVALUATION PAH (N=66) Good	• Vardenafil 5 mg daily, then 5 mg 2 times daily (N=44) • Placebo (N=22)	12	12, 24	• Mortality • 6MWD • Dyspnea • Functional class • Hospitalization • RHC • Adverse events

6MWD = 6 minute walk distance; IPAH = idiopathic PAH; mg = milligram; PAH = pulmonary arterial hypertension; PH = pulmonary hypertension; PPH = Primary pulmonary hypertension; RHC = right heart catheterization; SCD = scleroderma

[a]Outcome not assessed at 12 or 16 weeks.

[b]53 percent of patients received bosentan as background therapy.

Nonrandomized Comparative Observational Studies

We identified 9 nonrandomized observational studies involving 579 patients.[119,201-208] Of these, all were case series studies rated fair quality (Table 24). Four studies were retrospective, and five collected data prospectively. Epoprostenol was evaluated in six studies; iloprost, bosentan, treprostinil, and sildenafil in two studies each. Four studies directly compared two different monotherapies: one study compared bosentan with iloprost, two studies compared epoprostenol with treprostinil, and one study compared epoprostenol with iloprost. One study compared the combination of first-line epoprostenol and bosentan with epoprostenol monotherapy.

We do not discuss these nonrandomized comparative studies further in this report because the size and quality of the nonrandomized comparative studies compared poorly with the randomized trial data we identified. Although these studies offer the potential to address certain between-treatment comparisons that were not evaluated in RCTs and, in some cases, describe a longer duration of followup beyond that reported in the randomized trials, we assessed their limitations of poorly specified comparison (control) treatments and selection bias in treatment allocation combined with a lack of power from small size so severe as to make these data unusable.

Table 24. Study characteristics table for KQ 3 (nonrandomized studies)

Study Study Type Population (N) Quality	Study Arms (N)	Study Review Range	Followup Assessments (Months)	Outcome Measures
Higenbottam, 1993[208] Prospective case series Severe pulmonary hypertension Fair	• Epoprostenol, initial mean dose 5.2 (0.5) ng/kg/min, then titrated up to mean 18.7 (4.5) ng/kg/min (N=25) • No epoprostenol (N=19)	6-year period before 1993	12, 24, 36, 48	• Mortality • Progression to transplant
Fix, 2007[201] Retrospective case series Porto-pulmonary hypertension (N=36) Fair	• Epoprostenol 1 ng/kg/min, then titrated to mean dose of 29 ng/kg/min (N=19) • Non-epoprostenol (N=17)	1998–2005	2 to 95	• Mortality • RHC • Adverse events
Hoeper, 2007[202] Retrospective case series Porto-pulmonary hypertension and cirrhosis (N=31) Fair	• Bosentan 62.5 mg 2 times daily x 4 weeks, then 125 mg 2 times daily thereafter (N=18) • Aerosolized iloprost 5 mcg 6 times daily (N=13)	1999–2004	3, 6, 12, 18, 24, 30, 36	• Mortality • 6MWD • Functional class • Event-free survival • RHC • Adverse events

Table 24. Study characteristics table for KQ 3 (nonrandomized studies) (continued)

Study Study Type Population (N) Quality	Study Arms (N)	Study Review Range	Followup Assessments (Months)	Outcome Measures
Sastry, 2007[204] Prospective case series IPAH (N=178) Fair	• Conventional therapy (historical control) (N=39) • Conventional therapy + sildenafil 25-50 mg 3 times daily (N=139)	1999–2005	12, 24, 36, 48, 60	• Mortality
Jacobs, 2009[119] Prospective case series IPAH (N=16) Fair	• Epoprostenol titrated to 6-8 ng/kg/min after 1 week (N=6) • Treprostinil gradually increased to 10 ng/kg/min after 1 week, then 20 ng/kg/min after 6 weeks (N=10)	2002–2007	4, 6	• Mortality • 6MWD • Functional class • Natriuretic peptides • Adverse events
Reichenberger, 2011[203] Prospective case series IPAH, PAH, portopulmonary hypertension (N=24) Fair	• Epoprostenol gradually increased to maximum tolerated dose (N=12) • Aerosolized iloprost gradual titration up to 20 mcg per breath, maximum 120 mcg total daily dose (N=12)	NR	3, 12, 18, 20	• Mortality • 6MWD • Functional class • RHC • Progression to transplant • Adverse events
Zeng, 2011[205] Retrospective case series IPAH (N=77) Fair	• Conventional therapy (N=26) • Sildenafil 25 mg 3 times daily (N=51)	2005–2009	12, 24, 36	• Mortality • 6MWD • Dyspnea • RHC • BNP
Kemp, 2012[206] Retrospective case series Idiopathic, heritable, or anorexigen-associated PAH (N=69) Fair	• Epoprostenol/bosentan combined (n=23) • Epoprostenol monotherapy (n=46)	2001–2008	96	• Mortality • 6MWD • Functional class • RHC
Rich, 2012[207] Prospective cohort PAH (N=120) Fair	• IV Treprostinil in Epoprostenol diluent (n=25) • IV Epoprostenol in Epoprostenol diluent (n=61) • IV Treprostinil in native diluent (n=34)	2009–2010	NR (56,563 treatment days)	• Adverse events

6MWD = 6 minute walk distance; BNP = brain natriuretic peptide; IPAH = idiopathic PAH; IV = intravenous; mcg=microgram; NR = not reported; PAH = pulmonary arterial hypertension; RHC = right heart catheterization

Detailed Synthesis of Randomized Controlled Trials

We report on the outcomes of mortality, 6MWD, hospitalization, PVR, mPAP, cardiac index, and certain adverse reactions (headache, dizziness, diarrhea, peripheral edema, jaw pain, flushing, cough, and infections) for the following comparative analyses of pharmacotherapies:

- Head-to-head comparisons by individual drug, when available
- Monotherapy versus placebo (or monotherapy plus standard therapy vs. standard therapy alone) by individual drug
- Monotherapy versus placebo (or monotherapy plus standard therapy vs. standard therapy alone) by class of drug
- Combination therapy versus monotherapy by individual drug

The latter three comparative analyses are reported in tabular and graphic form in a single forest plot for each outcome. We also conducted meta-analyses and reported summary measures for the analyses by individual drug (e.g., studies of bosentan vs. placebo) and class of drug (e.g., prostacyclin-analogues vs. placebo or standard therapy) whenever there were two or more studies with comparable study arms.

We use the term background treatment for cointerventions that are preexisting and applied to both study arms of an RCT in which a second (new) drug is added to one arm (experimental) but not the other (control). Thus, the trial of iloprost plus bosentan versus bosentan (e.g., COMBI[192]) would be described as a trial of iloprost with bosentan background therapy and can be construed to examine the efficacy of combination versus monotherapy; it is also relevant to the efficacy of iloprost. In our meta-analyses, we would infer efficacy of iloprost from controlled trials of iloprost both with and without background therapy. This, however, assumes independent and additive effects of the experimental drug relative to any or all of the other background therapies received by the patients enrolled in the trial (including, but not limited to, other PAH-specific drugs, supplemental oxygen, vasodilators, etc.). We did not identify any eligible studies that randomized treatment- naïve patients to monotherapy versus combination therapy, or that randomized treatment-naïve patients to combination therapy versus placebo or standard therapy. In each of the five combination therapy versus monotherapy studies included in this report, combination therapy refers to the step-wise addition of a second drug to existing monotherapy.

Mortality

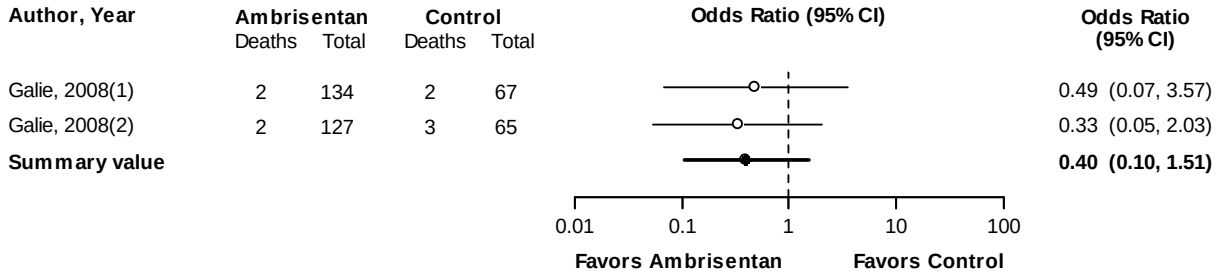
We identified a single head-to-head, double-blind RCT that compared bosentan with sildenafil in patients with PAH.[156] One of the 14 patients in the sildenafil group died during the fourteenth week of treatment. There were no deaths among the 12 patients in the bosentan group during the 16-week intervention period. A total of 20 RCTs reported the effects of monotherapy or compared to placebo, standard therapy, or combination therapy for PAH on mortality outcomes. For two of the studies[188,193] (including ASSET-2, but not including ASSET-1, both of which were reported in the paper by Barst et al.[188]), no deaths were reported, so an odds ratio for mortality could not be calculated. Therefore, 18 studies (14 monotherapy and 4 combination therapy) consisting of a total of 3077 patients were included for analysis, as follows:

- 2 studies (represented by 1 article) compared ambrisentan with placebo[106]
- 3 studies compared bosentan with placebo[182,184,185]
- 3 studies compared IV epoprostenol with standard therapy[85,181,194]
- 2 studies compared aerosolized iloprost with placebo[190,191]
- 1 study compared sildenafil with placebo[187]
- 1 study compared 4 doses of tadalafil with placebo, with 53% of patients receiving bosentan as background therapy[196]
- 2 studies compared IV or subcutaneous treprostinil with placebo[197,199]
- 1 study compared vardenafil with placebo[200]
- 3 studies compared combination therapy with monotherapy[131,186,189]

Ambrisentan Versus Placebo

Figure 23 shows the forest plot of the odds ratio for mortality for treatment with ambrisentan versus placebo from 2 studies (393 patients). Each of these studies involved two active doses of ambrisentan between 2.5 mg to 10 mg daily with a 5 mg dose used in both studies. Our analysis combined active doses in each study. The duration of treatment was 12 weeks in both studies. The individual odds ratios for the two studies were 0.33 and 0.49, with a summary odds ratio of 0.40 (95% CI, 0.10 to 1.51). The comparative efficacy of ambrisentan in reducing mortality compared with placebo is inconclusive given the small number of trials, the wide confidence intervals, and the observation that the confidence interval includes 1.0.

Figure 23. Forest plot of odds ratio for mortality—ambrisentan versus placebo

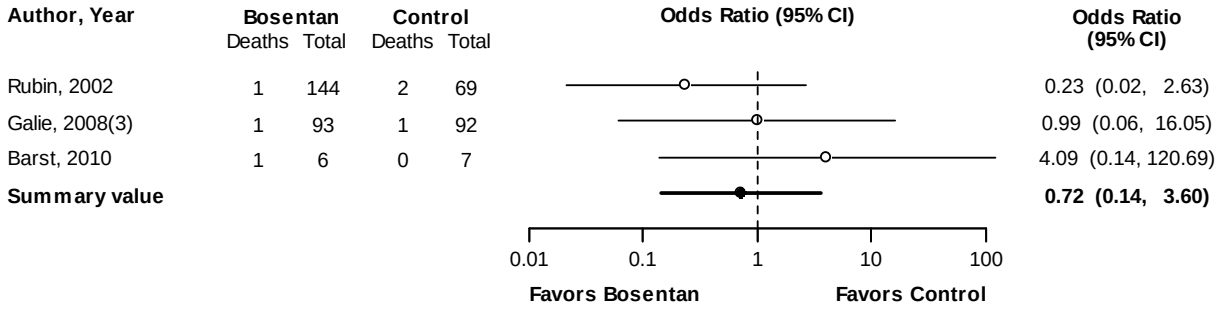


CI = confidence interval

Bosentan Versus Placebo

Figure 24 shows the forest plot of the odds ratio for mortality for treatment with bosentan versus placebo from 3 studies (411 patients). The dosages of bosentan across the trials were similar (62.5 mg two times daily titrated up to 125–250 mg two times daily). The duration of treatment ranged from 16 to 32 weeks. The individual odds ratios ranged from 0.23 to 4.09, with a summary odds ratio of 0.72 (95% CI, 0.14 to 3.60). The comparative efficacy of bosentan in reducing mortality compared with placebo is inconclusive given the small number of trials, wide confidence intervals, and the observation that the confidence interval includes 1.0.

Figure 24. Forest plot of odds ratio for mortality—bosentan versus placebo

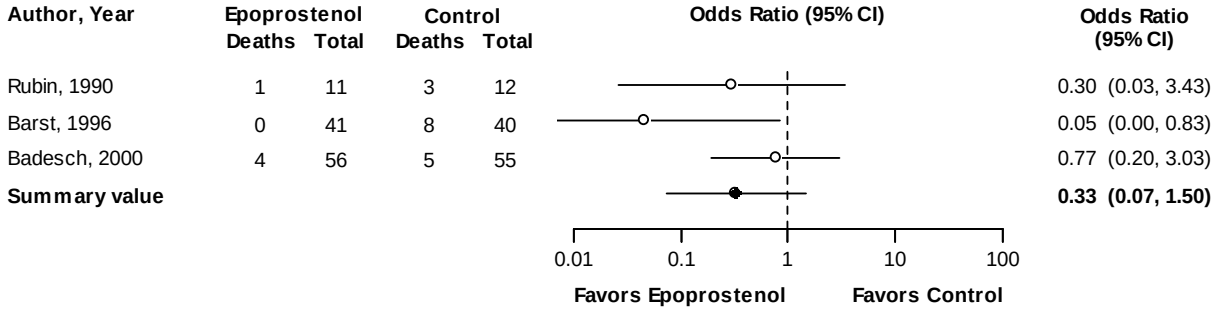


CI = confidence interval

Epoprostenol Versus Standard Therapy

Figure 25 shows the forest plot of the odds ratio for mortality for treatment with intravenous epoprostenol versus standard therapy from three studies (215 patients). The duration of therapy ranged from 8 to 12 weeks. The individual odds ratios ranged from 0.05 to 0.77, with a summary odds ratio of 0.33 (95% CI, 0.07 to 1.50). The comparative efficacy of epoprostenol in reducing mortality compared with standard therapy is inconclusive given the small number of trials, the wide confidence intervals, and the observation that the confidence interval includes 1.0.

Figure 25. Forest plot of odds ratio for mortality—intravenous epoprostenol versus standard therapy

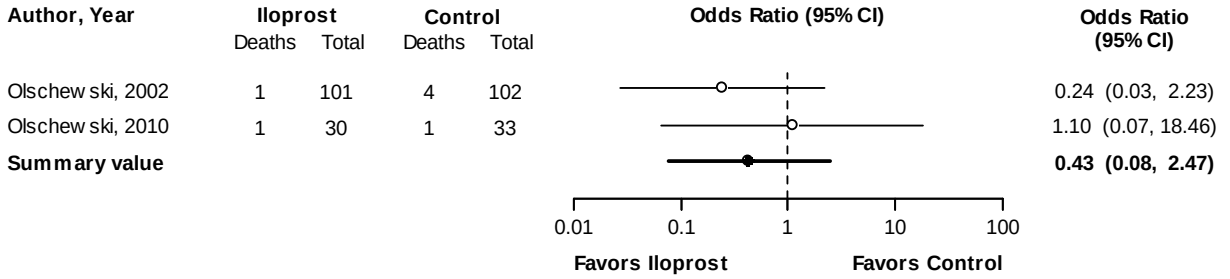


CI = confidence interval

Iloprost Versus Placebo

Figure 26 shows the forest plot of the odds ratio for mortality for treatment with aerosolized iloprost versus placebo from two studies (266 patients). Both studies contained patient groups diagnosed with non-Class 1 PH. The duration of therapy was 12 weeks in both studies. The doses of aerosolized iloprost were between 2.5 and 5.0 micrograms delivered from six to nine times daily with dosage and schedules individualized based on a predetermined algorithm. The individual odds ratios for the two studies were 0.24 and 1.10, with a summary odds ratio of 0.43 (95% CI, 0.08 to 2.47). The comparative efficacy of iloprost in reducing mortality compared with placebo is inconclusive given the small number of trials, the wide confidence intervals, and the observation that the confidence interval includes 1.0.

Figure 26. Forest plot of odds ratio for mortality—aerosolized iloprost versus placebo



CI = confidence interval

Sildenafil Versus Placebo

A single eligible study compared sildenafil with placebo.[187] The SUPER study was a good-quality, 4-arm RCT that compared three dosages of sildenafil (20 mg, 40 mg, and 80 mg daily) with placebo. The 4 deaths among 277 patients reported over the course of the 3-month study were distributed relatively evenly across the 4 study arms.

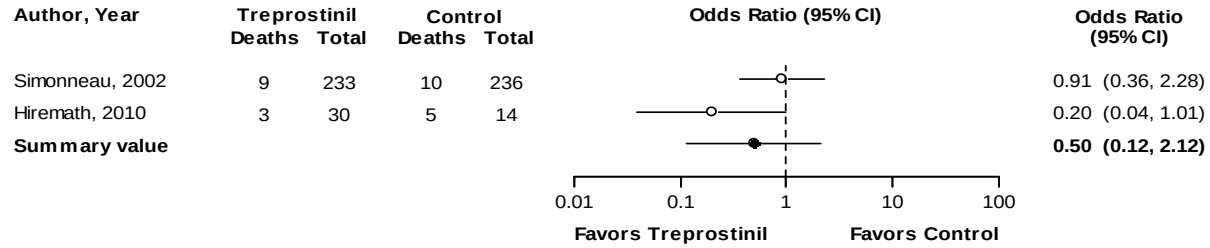
Tadalafil Versus Placebo

A single eligible study compared tadalafil with placebo.[196] The PHIRST study was a good-quality, five-arm RCT that compared four doses of tadalafil (2.5 mg, 10 mg, 20 mg, and 40 mg daily) with placebo. Fifty-three percent of patients in this study also received bosentan as background therapy; limited data were reported for this subgroup of patients which prevented including this study as a test of combination versus monotherapy[209]. Three deaths were reported within the first 16 weeks of treatment among the 405 patients in this study: 1 in the placebo group, 1 in the 10 mg tadalafil group; and 1 in the 20 mg tadalafil group.

Treprostinil Versus Placebo

Figure 27 shows the forest plot of the odds ratio for mortality for treatment with treprostinil versus placebo from two studies (513 patients). The duration of treatment was 12 weeks in both studies. The method of infusion was different between the studies (intravenous versus subcutaneous). The individual odds ratios were 0.20 and 0.91, with a summary odds ratio of 0.50 (95% CI, 0.12 to 2.12). The comparative efficacy of treprostinil in reducing mortality compared with placebo is inconclusive given the small number of trials, the wide confidence intervals, and the observation that the confidence interval includes 1.0.

Figure 27. Forest plot of odds ratio for mortality—treprostinil versus placebo



CI = confidence interval

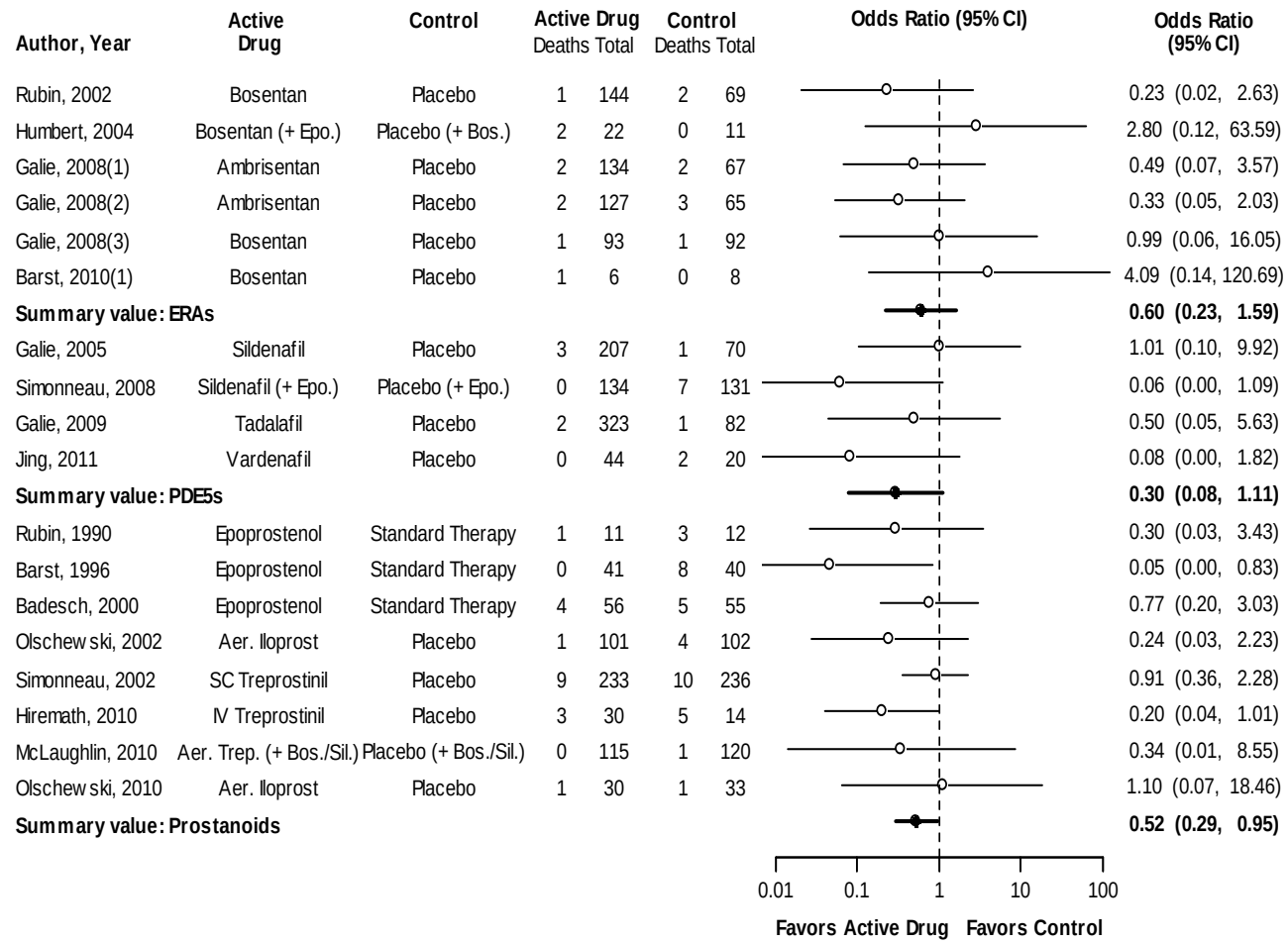
Vardenafil Versus Placebo

A single eligible study compared vardenafil with placebo.[200] The EVALUATION study was a good-quality, RCT that compared vardenafil 5 mg daily (later increased to 5 mg 2 times daily) with placebo. Over the course of the 3-month study period, two deaths were observed among the 20 patients in the placebo arm, compared with zero deaths among the 44 patients in the active treatment arm.

Mortality by Drug Class

Figure 28 shows the forest plot of the odds ratio for mortality by drug class. Incidence of death after 8 to 16 weeks of treatment was decreased by treatment with prostanoids compared with standard therapy or placebo (OR 0.52; 95% CI, 0.29 to 0.95). Similar point estimates for odds ratios were observed for endothelin antagonists (OR 0.60; CI, 0.23 to 1.59) and phosphodiesterase inhibitors (OR 0.30; CI, 0.08 to 1.11), but the confidence intervals were wide and included 1.0. There was little evidence of statistical heterogeneity among the six studies of endothelin antagonists, with a Q-value of 3.33 for 5 degrees of freedom, I^2=0, p=0.65; among the four studies of phosphodiesterase inhibitors, with a Q-value of 3.11 for 3 degrees of freedom, I2=3%, p=0.38 or among the 8 studies of prostanoids, with a Q-value of 6.75 for 7 degrees of freedom, I^2=0, p=0.46.

Figure 28. Forest plot of odds ratio for mortality by drug class



Aer = aerosolized; Bos = bosentan; CI = confidence interval; Epo = epoprostenol; ERA = endothelin receptor antagonist; IV = intravenous; PDE5 = phosphodiesterase type 5 inhibitor; SC = subcutaneous; Sil = sildenafil; Trep = treprostinil

Combination Therapy Versus Monotherapy

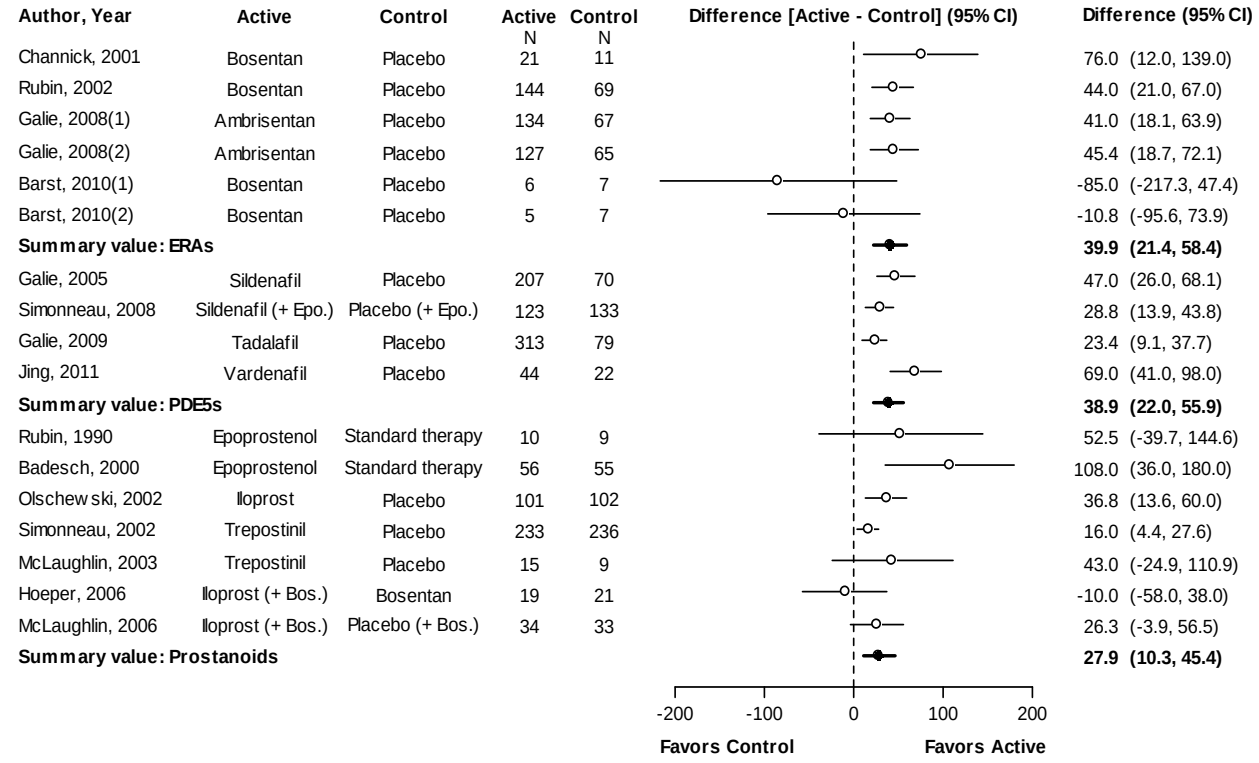
Three studies representing 566 patients evaluated mortality associated with combination therapy versus mortality associated with monotherapy. The therapies differed between studies: sildenafil plus IV epoprostenol versus IV epoprostenol plus placebo, bosentan plus IV epoprostenol versus IV epoprostenol plus placebo, and bosentan or sildenafil plus aerosolized treprostinil versus bosentan or sildenafil plus placebo. The duration of treatment ranged from 12 to 16 weeks. The individual odds ratios ranged from 0.06 to 2.80, with a summary odds ratio of 0.37 (95% CI, 0.04 to 3.32). The comparative efficacy of combination therapy in reducing mortality compared with monotherapy is inconclusive given the small number of trials, the wide confidence intervals, and the observation that the confidence interval includes 1.0.

6-Minute Walk Distance (6MWD)

A total of 17 RCTs representing 2587 patients reported the effects of monotherapy or combination therapy for PAH on 6MWD at 8 to 16 weeks after initiating treatment.[94,106,181,182,185,187,189,190,192-194,196-198,200] In addition, one study compared bosentan with sildenafil.[156] Two studies compared bosentan with placebo.[94,182] One article reporting the results of two studies compared ambrisentan with placebo.[187] Two studies compared sildenafil with placebo,[187,189] one study compared tadalafil with placebo,[196] one study compared vardenafil with placebo,[200] and three studies compared iloprost with placebo.[190,192,193] Three of the 12 studies evaluated combination therapy versus monotherapy: 1 sildenafil study was conducted in patients with epoprostenol as background therapy,[189] and 2 iloprost studies were conducted in patients with bosentan as background therapy.[192,193] Twelve of the 17 studies were rated good quality, 4 were rated fair quality, and 1[192] was rated poor quality.

The single small, head-to-head comparison of bosentan versus sildenafil showed no statistically significant difference in 6MWD in an intention-to-treat analysis.[156] Figure 29 shows the forest plot of a meta-analysis of the 17 remaining studies. The analysis revealed a statistically significant improvement in 6MWD associated with each of the 3 drug classes. Endothelin antagonists, as a class, were associated with an improvement in 6MWD of 39.9 m (95% CI, 21.4 to 58.4) whereas phosphodiesterase inhibitors and prostanoids were associated with improvements of 38.9 m (CI, 22.0 to 55.9) and 27.9 m (CI, 10.3 to 45.4), respectively. There was moderate heterogeneity among these studies, with a Q-value of 7.68 for 5 degrees of freedom, I^2=34.89, p=0.17 for endothelin antagonists, a Q-value of 10.09 for 3 degrees of freedom, I^2=70.28, p=0.018 for phosphodiesterase inhibitors, and a Q-value of 11.02 for 6 degrees of freedom, I^2=45.57, p=0.088 for prostanoids.

Figure 29. Forest plot of effects of therapy by drug class on 6MWD



CI = confidence interval; ERA = endothelin receptor antagonist; PDE5 = phosphodiesterase type 5 inhibitor

Two good-quality studies[189,193] and one fair-quality study[192] involving 363 patients evaluated changes in 6MWD associated with combination therapy versus monotherapy. One study evaluated the efficacy of sildenafil with epoprostenol as background therapy, and two evaluated the efficacy of iloprost with bosentan as background therapy. The summary estimate of the difference in means for these 3 studies was 23.9 (95% CI, 8.0 to 39.9). This finding suggests a moderate improvement in 6MWD associated with combination therapy compared with monotherapy.

A fourth study provides additional information about the comparison of combination therapy versus monotherapy. Barst et al.[209] conducted a subgroup analysis of the PHIRST study, which was a 5-arm RCT that compared 4 doses of tadalafil with placebo. Of the 405 patients enrolled in that study, 215 (53%) were on bosentan as background therapy. The investigators authors reported mean change from baseline in 6MWD for the placebo arm and the study arm that received tadalafil 40 mg per /day at 8, 12, and 16 weeks, for both the patients on background bosentan and the patients who were treatment-naïve patients (only the 40 mg/day dose of tadalafil was reported because that was the only dose that showed significant differences in primary and secondary efficacy analyses). At the 16-week assessment, the mean change in 6MWD was 40.2 m (95% CI, 23.1 to 57.2) among patients on background therapy who received tadalafil 40 mg per day; 18.8 m (CI, 0.5 to 37.2) for patients on background therapy who received placebo; 42.2 m (CI, 26.7 to 57.5) for treatment-naïve patients on tadalafil 40 mg per day; and -2.9 m (CI, -22.8 to 17.1) for treatment-naïve patients on placebo. This corresponds to a placebo-corrected difference of 21.4 m among patients on background bosentan and 45.1 m

among treatment-naïve patients. This non-randomized comparison (without testing for statistical significance testing) tentatively suggests that 6MWD improvement associated with monotherapy with 40 mg per day of tadalafil after 16 weeks of treatment may be greater than the improvement in 6MWD associated with adding tadalafil to an existing treatment regimen that includes bosentan. These limited and potentially confounded data suggest that monotherapy may have a greater effect on 6MWD relative to adding a second treatment to existing background therapy. Interpretation of these findings is further complicated by important differences between groups at baseline, including the observation that 74 percent of treatment-naïve patients had a duration of PAH of less than 2 years compared with 38 percent of patients on bosentan background therapy.

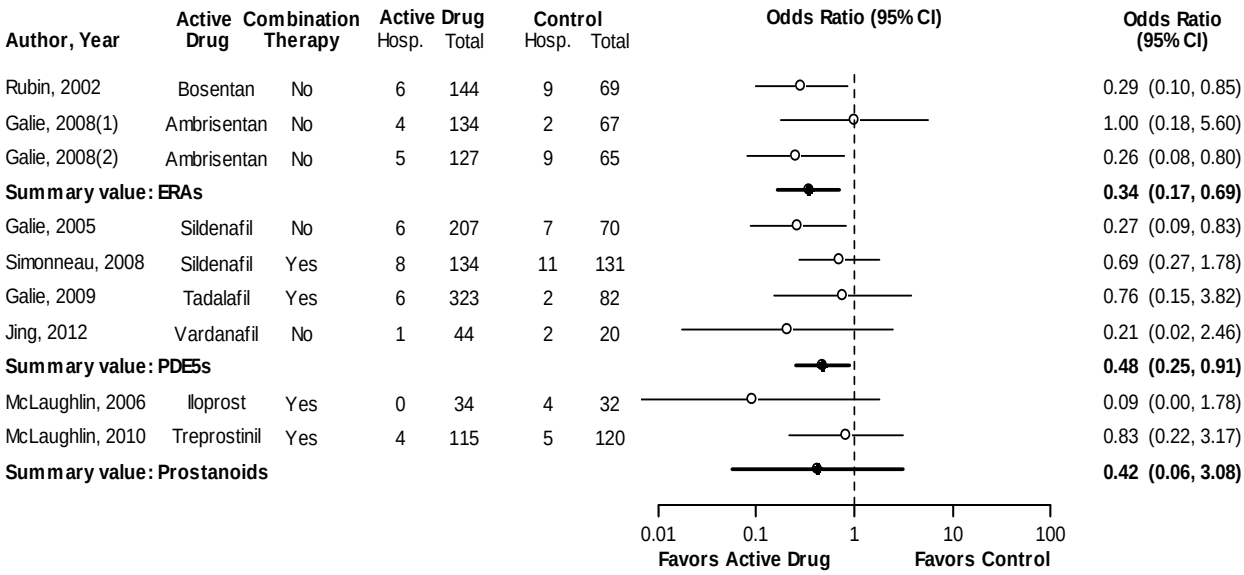
We created a funnel plot that included the 17 RCTs reported in Figure 29. Visual inspection of this funnel plot suggested an absence of publication bias. We used 6MWD to evaluate for possible publication bias because it is the outcome that was most commonly reported among the studies included in this report.

Hospitalization

A total of 9 RCTs representing 1918 patients reported the effects of monotherapy or combination therapy for PAH on hospitalization for worsening of PAH within 8 to 16 weeks after initiating treatment (Figure 30).[106,131,182,187,189,193,196,200] One study compared bosentan with placebo,[182] one article reporting the results of two studies compared ambrisentan with placebo,[106] two studies compared sildenafil with placebo[187,189] (one with epoprostenol as background therapy), one study compared tadalafil with placebo,[196] one study compared vardenafil with placebo,[200] one study compared iloprost with placebo with bosentan as background therapy[193] and one study compared treprostinil with placebo.[131] All nine studies were rated good quality. Meta-analysis of these studies revealed a statistically significant reduction in hospitalization associated with endothelin antagonists (OR 0.34; 95% CI, 0.17 to 0.69) and phosphodiesterase inhibitors (OR 0.48; CI, 0.25 to 0.91) while data on prostanoids were inconclusive (OR 0.42; CI, 0.06 to 3.08). There was little evidence of statistical heterogeneity among the 4 studies involving endothelin antagonists, with a Q-value of 2.34 for 3 degrees of freedom, I^2=0, p=0.51.

Three good-quality studies[131,189,193] involving 566 patients evaluated hospital admissions due to worsening PAH symptoms associated with combination therapy versus monotherapy. One study evaluated the efficacy of sildenafil with epoprostenol as background therapy, one evaluated the efficacy of iloprost with bosentan as background therapy, and one evaluated the efficacy of treprostinil with bosentan or sildenafil as background therapy. The summary estimate of the odds ratios for these 3 studies was 0.64 (95% CI, 0.31 to 1.36). This represents insufficient evidence to conclude whether combination therapy and monotherapy differ in their effects on hospitalization incidence during the first 2 to 4 months of treatment.

Figure 30. Forest plot of effects of therapy by drug class on hospitalization



CI = confidence interval; ERA = endothelin receptor antagonist; PDE5 = phosphodiesterase type 5 inhibitor

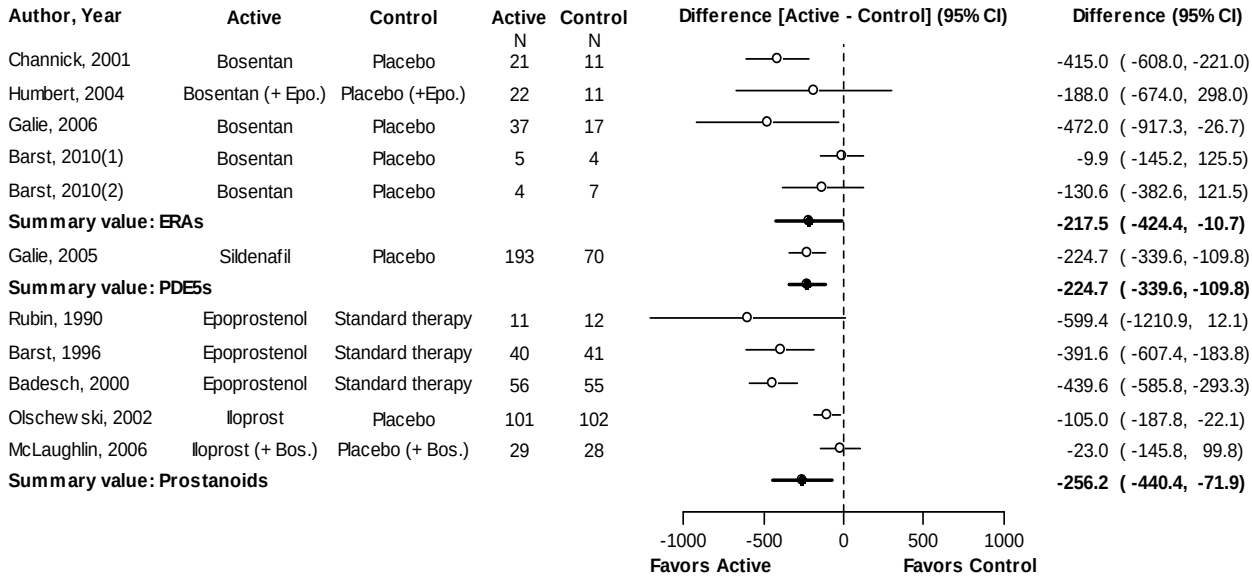
Pulmonary Vascular Resistance

A total of 11 RCTs representing 877 patients reported the effects of monotherapy or combination therapy for PAH on PVR as assessed by right heart catheterization at 8 to 16 weeks after initiating treatment (Figure 31).[85,94,181,183,185-187,190,193,194]

Four studies compared bosentan with placebo,[94,183,185] one study compared bosentan plus epoprostenol to epoprostenol plus placebo,[186] one study compared iloprost with placebo,[190] one study compared iloprost plus bosentan with bosentan plus placebo,[193] four studies compared epoprostenol with standard therapy,[85,181,194] and one study compared sildenafil with placebo.[187] Eight studies were rated good quality and three fair quality.[185,194]

Figure 31 shows the forest plot of the 11 RCTs with meta-analysis by drug class. Meta-analysis of the five studies that evaluated an endothelin antagonist as the active treatment showed a summary estimate of -217.5 mm Hg/liter/min (95% CI, -424.4 to -10.7). Heterogeneity was very high, with a Q-value of 15.87 for 3 degrees of freedom, I^2=74.79%, p=0.003. The single study that evaluated a phosphodiesterase inhibitor (sildenafil) reported an improvement in PVR associated with active treatment of -224.7 mm Hg/liter/min (CI, -339.6 to -109.8). Meta-analysis of the five studies that evaluated a prostanoid as the active treatment demonstrated an improvement in PVR associated with active treatment of -256.2 mm Hg/liter/min (CI, -440.4 to -71.9). Heterogeneity was very high, with a Q-value of 27.96 for 4 degrees of freedom, I^2=85.7%, p<0.001. Only two studies compared combination therapy with monotherapy using PVR as assessed by right heart catheterization as an outcome at 8 to 16 weeks after initiating treatment. The summary estimate of the difference in means for these two studies was -33.2 (CI, -149.5 to 83.1).

Figure 31. Forest plot of effects of therapy by drug class on pulmonary vascular resistance



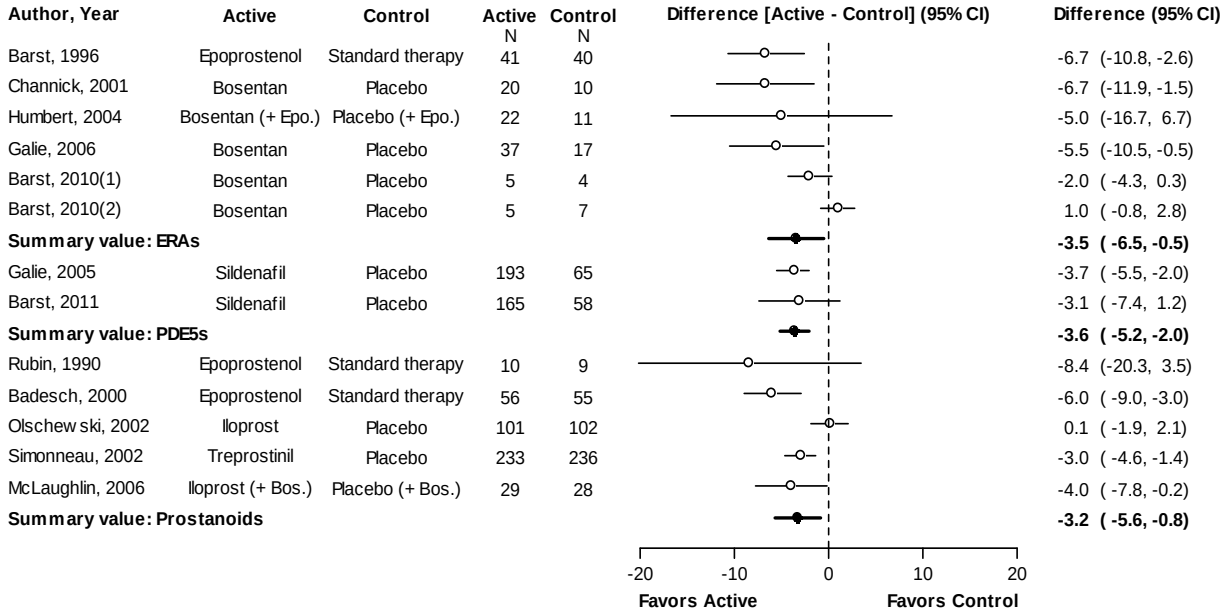
CI = confidence interval; ERA = endothelin receptor antagonist; PDE5 = phosphodiesterase type 5 inhibitor

Mean Pulmonary Artery Pressure

Thirteen RCTs representing 1559 patients reported mPAP as assessed by RHC 8 to 16 weeks after initiation of treatment.[85,94,181,183,185-188,190,193,194,197] Six studies evaluated an endothelin antagonist, two studies evaluated the phosphodiesterase inhibitor sildenafil, and five studies evaluated a prostanoid. Two studies were combination therapy studies: one compared bosentan plus epoprostenol with placebo and epoprostenol,[186] and one compared iloprost plus bosentan with placebo plus bosentan.[193] Nine studies were rated good quality and four fair quality.

Figure 32 shows the forest plot of a meta-analysis by drug class, which revealed significant improvement in mPAP for all three drug classes. The summary change in mean arterial pressures were -3.5 mmHg (95% CI, -6.5 to -0.5) for endothelin antagonists, -3.6 mmHg (CI, -5.2 to -2.0) for phosphodiesterase inhibitors (sildenafil only), and -3.2 mmHg for prostanoids (CI, -5.6 to -0.8). There was high heterogeneity among the 6 studies of endothelin antagonists, with a Q-value of 23.3 for 5 degrees of freedom, I^2=78.5%, p<0.001, and high heterogeneity among the 5 studies of prostanoids, with a Q-value of 13.85 for 4 degrees of freedom, I^2=71.13%, p=0.008. Only two studies compared combination therapy with monotherapy using mPAP as an outcome at 8 to 16 weeks after initiating treatment. The summary estimate of the difference in means for these two studies was -4.1 (95% CI, -7.6 to -0.6).

Figure 32. Forest plot of effects of therapy by drug class on mean pulmonary artery pressure (mPAP)



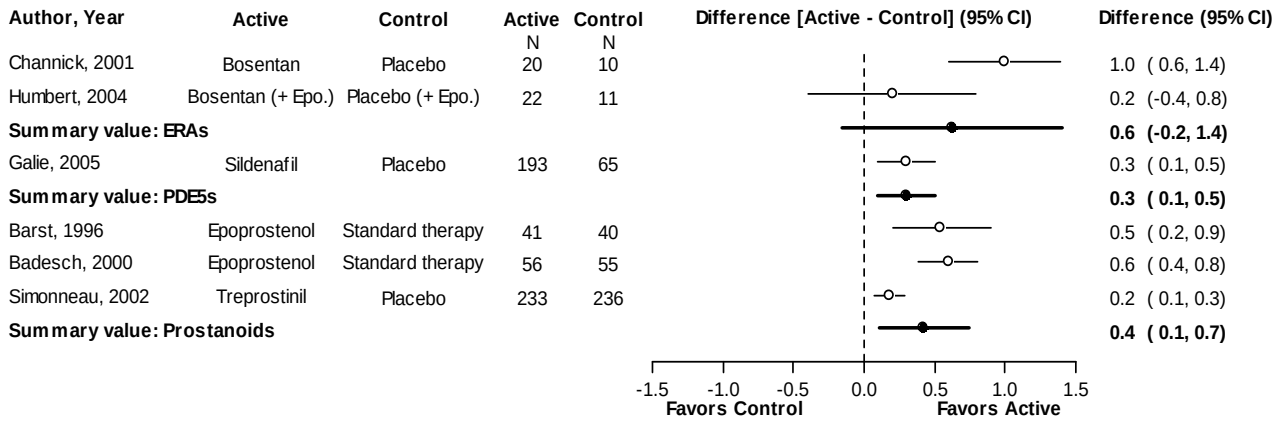
Bos = bosentan; CI = confidence interval; Epo = epoprostenol; ERA = endothelin receptor antagonist; PDE5 = phosphodiesterase type 5 inhibitor

Cardiac Index

A total of 6 RCTs representing 982 patients reported cardiac index assessed 8 to 16 weeks after initiation of treatment compared with placebo or standard therapy (Figure 33).[85,94,156,187,194,197] One good-quality study compared bosentan with placebo,[94] one good-quality study compared bosentan plus epoprostenol with epoprostenol plus placebo,[186] one good-quality and one fair-quality study compared epoprostenol with standard therapy,[85,194] one good-quality study compared three doses of sildenafil with each other and with placebo,[187] and one good quality study compared subcutaneous treprostinil with placebo.[197] An additional good-quality study was a head-to-head trial that compared bosentan with sildenafil.[156]

The single RCT that compared bosentan with placebo demonstrated a significant improvement in cardiac index of 1.0 L per minute per meter-squared (95% CI, 0.6 to 1.4) at 12 weeks, in favor of bosentan. The single study that compared sildenafil with placebo permitted dose comparisons; each of the 3 doses (20, 40, and 80 mg three times daily) was associated with statistically significant improvement in cardiac index. Combining the data from all three sildenafil doses generated a summary estimate of an improvement in cardiac index associated with sildenafil versus placebo at 12 weeks of 0.3 L per minute per meter-squared (CI, 0.1 to 0.5). Meta-analysis of the three studies that evaluated a prostanoid generated a summary estimate for improvement in cardiac index of 0.4 L per minute per meter-squared (CI, 0.1 to 0.7) at 12 weeks.

Figure 33. Forest plot of effects of therapy by drug class on cardiac index



CI = confidence interval; Epo = epoprostenol; ERA = endothelin receptor antagonist; PDE5 = phosphodiesterase type 5 inhibitor

Adverse Events

Adverse events that occurred during the first 8 to 16 weeks after initiation of treatment were reported in 21 of the 28 RCTs that compared an endothelin antagonist, phosphodiesterase inhibitor, or prostanoid with either placebo or standard therapy. Adverse events were not reported in the single RCT that compared two active therapies.[156] The most commonly assessed and reported adverse events were headache, dizziness, diarrhea, peripheral edema, jaw pain, flushing, and cough.

For these studies, we computed a summary estimate for the odds ratio for each of three classes of drugs: (1) endothelin antagonists, (2) phosphodiesterase inhibitors, and (3) prostanoids. We computed separate summary estimates for the odds ratio of all prostanoids versus prostanoids delivered via an aerosolized route of administration. An odds ratio greater than 1.0 indicates a higher incidence of adverse events associated with active treatment, and an odds ratio less than 1.0 indicates a lower incidence of adverse events associated with active treatment. When combination therapy was compared with monotherapy, an odds ratio greater than 1.0 indicates a higher incidence of adverse events associated with monotherapy.

Headache

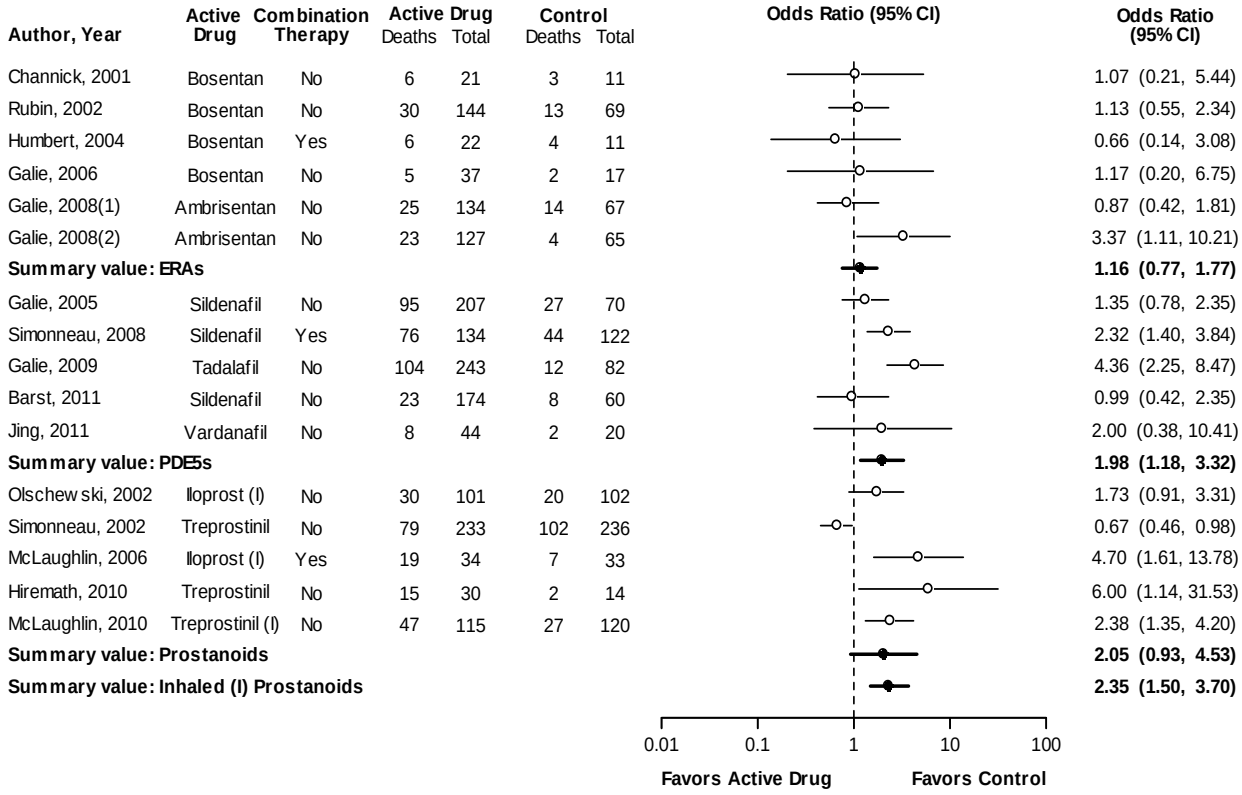
A total of 16 RCTs representing 2899 patients assessed the incidence of headache within the first 8 to 16 weeks of initiating therapy (Figure 34).[94,106,131,182,183,186-190,193,196,197,199,200] Fourteen studies were rated good quality and two fair quality. There was moderate heterogeneity among these studies, with a Q-value of 36.3 for 14 degrees of freedom, I^2=61.4%, p<0.001. Meta-analysis of 6 good-quality studies of endothelin antagonists involving 780 patients yielded a summary odds ratio of 1.16 (95% CI, 0.77 to 1.77). There was a two-fold higher incidence of headache among patients treated with phosphodiesterase inhibitors compared with placebo or standard therapy (OR 1.98; CI, 1.18 to 3.32). The 95-percent confidence interval for the summary odds ratio associated with all prostanoids includes 1.0 (CI, 0.93 to 4.53), but there was a significantly higher incidence of headache among patients treated with aerosolized prostanoids (OR 2.35; CI, 1.50 to 3.70).

There was little evidence of statistical heterogeneity among the 6 studies of endothelin antagonists, with a Q-value of 4.7 for 5 degrees of freedom, I^2=0, p<0.45 and high heterogeneity among both the 4 studies of phosphodiesterase inhibitors, with a Q-value of 10.13 for 4 degrees

of freedom, I^2=60.51%, p<0.038, and the 4 studies of prostanoids, with a Q-value of 25.68 for 4 degrees of freedom, I^2=84.42%, p<0.001.

Three good-quality studies[186,189,193] involving 356 patients evaluated the incidence of headache associated with combination therapy versus monotherapy. One study evaluated the efficacy of bosentan with epoprostenol as background therapy, one compared sildenafil with placebo with epoprostenol as background therapy, and one evaluated the efficacy of iloprost with bosentan as background therapy. We did not estimate a summary estimate for the odds ratio for headache associated with combination therapy compared with monotherapy because of the high degree of heterogeneity between studies, including the use of different drugs for both active and background therapy.

Figure 34. Forest plot of effects of therapy by drug class on headache



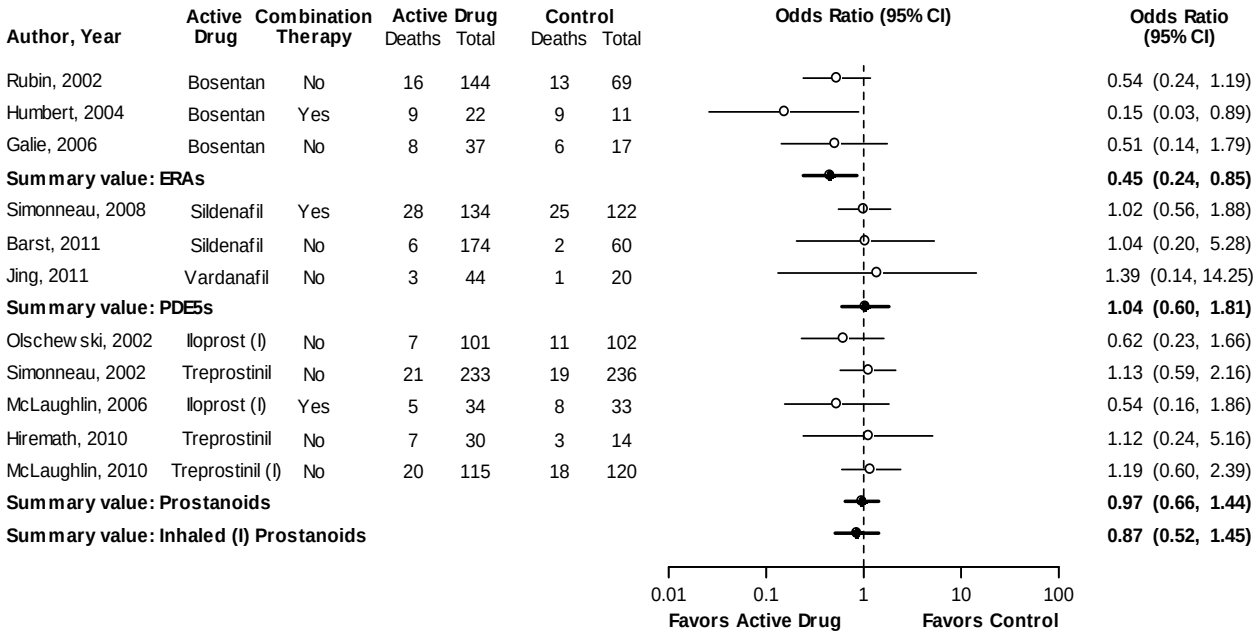
CI = confidence interval; ERA = endothelin receptor antagonist; PDE5 = phosphodiesterase type 5 inhibitor

Dizziness

A total of 11 RCTs representing 1872 patients assessed the incidence of dizziness within the first 8 to 16 weeks of initiating therapy (Figure 35).[131,182,183,186,188-190,193,197,199,200] Nine studies were rated good quality and two fair quality. With the exception of one small study[186] that reported a higher incidence of dizziness in the in the epoprostenol plus bosentan study arm compared with the epoprostenol plus placebo arm, there were no statistically significant differences in the proportion of patients reporting adverse events between active and control groups across in any of the individual studies, or within drug class. Meta-analysis of 3 good-quality studies of endothelin antagonists involving 300 patients yielded a summary odds ratio of 0.45 (95% CI, 0.24 to 0.85). There was no apparent association between treatment of phosphodiesterase inhibitors (OR 1.04; CI, 0.60 to 1.81) or prostanoids (OR 0.97; CI, 0.66 to 1.44) and incidence of dizziness. There was little evidence of statistical heterogeneity among the 5 studies of prostanoids, with a Q-value of 2.26 for degrees of freedom, I^2=0, p=0.85.

Three good-quality studies[186,189,193] involving 356 patients evaluated the incidence of dizziness associated with combination therapy versus monotherapy. One study evaluated the efficacy of bosentan with epoprostenol as background therapy, one compared sildenafil with placebo with epoprostenol as background therapy, and one evaluated the efficacy of iloprost with bosentan as background therapy. We did not estimate a summary estimate for the odds ratio for dizziness associated with combination therapy compared with monotherapy because of the high degree of clinical heterogeneity between studies, including the use of different drugs for both active and background therapy.

Figure 35. Forest plot of effects of therapy by drug class on dizziness



CI = confidence interval; ERA = endothelin receptor antagonist; PDE5 = phosphodiesterase type 5 inhibitor

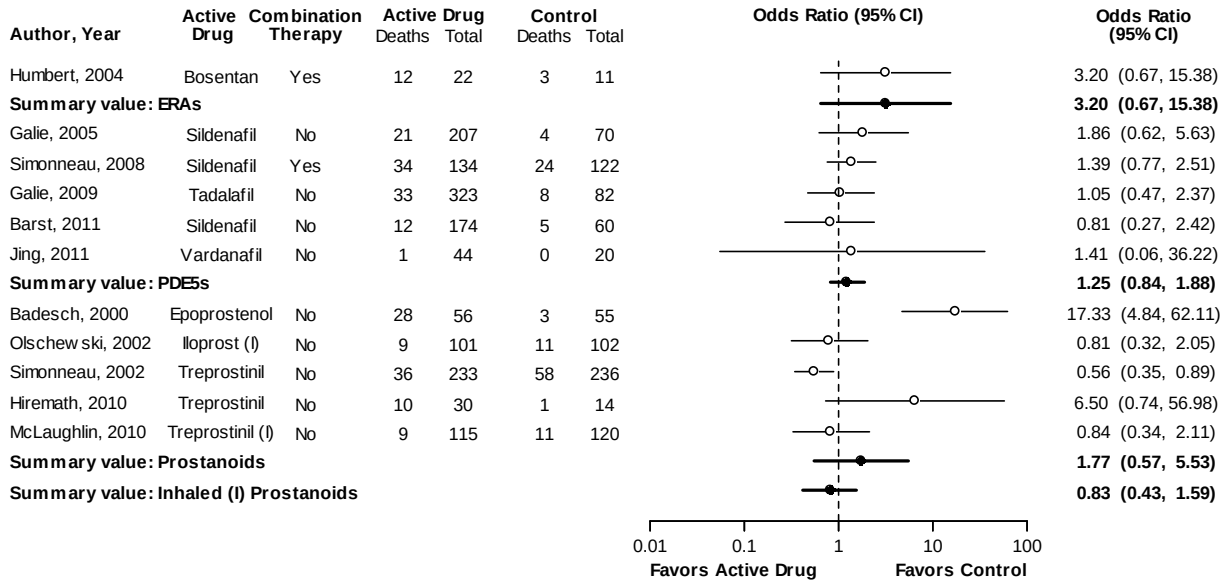
Diarrhea

A total of 11 RCTs representing 2331 patients assessed the incidence of diarrhea within the first 8 to 16 weeks of initiating therapy (Figure 36).[131,186-190,194,196,197,199,200] Eight studies were

rated good quality and three fair quality. Meta-analysis of these studies revealed no statistically significant differences in the proportion of patients reporting adverse events between active and control groups within any of the three drug class (OR 3.20; 95% CI, 0.67 to 15.38 for endothelin antagonists; OR 1.25; CI, 0.84 to 1.88 for phosphodiesterase inhibitors; and OR 1.77; CI, 0.57 to 5.53 for prostanoids). There was little evidence of statistical heterogeneity among the five studies of phosphodiesterase inhibitors, with a Q-value of 1.39 for 4 degrees of freedom, I^2=0, p<0.85, and high heterogeneity among the five studies of prostanoids, with a Q-value of 27.89 for 4 degrees of freedom, I^2=85.66%, p<0.001.

Two good-quality studies[186,189] involving 289 patients evaluated the incidence of diarrhea associated with combination therapy versus monotherapy. One study evaluated the efficacy of bosentan with epoprostenol as background therapy, one compared sildenafil with placebo with epoprostenol as background therapy, and one evaluated the efficacy of tadalafil with bosentan as background therapy. We did not estimate a summary estimate for the odds ratio for diarrhea associated with combination therapy compared with monotherapy because of the high degree of heterogeneity between studies, including the use of different drugs for both active and background therapy.

Figure 36. Forest plot of effects of therapy by drug class on diarrhea



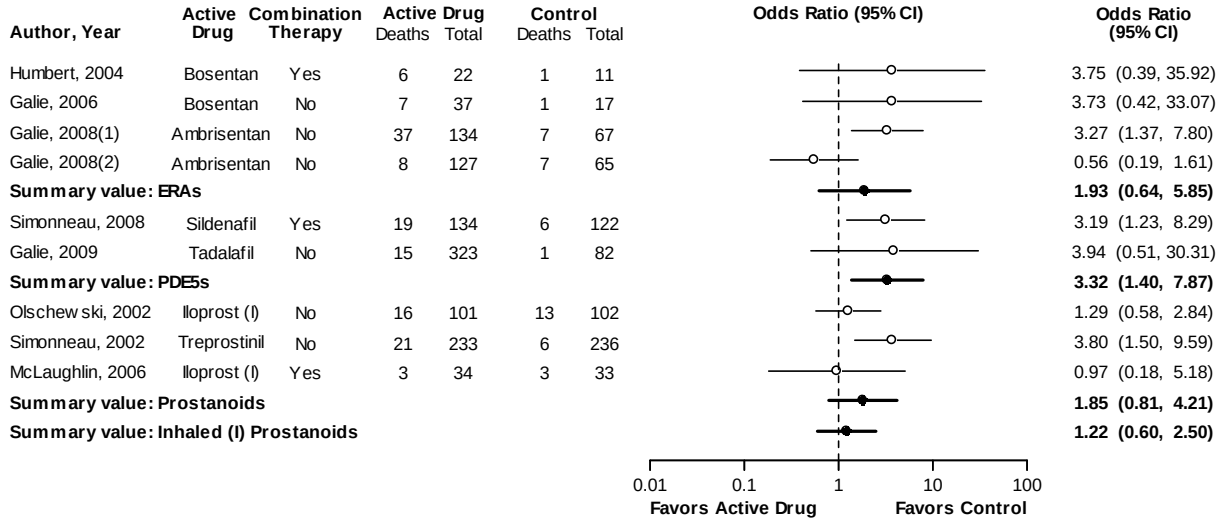
CI = confidence interval; ERA = endothelin receptor antagonist; PDE5 = phosphodiesterase type 5 inhibitor

Peripheral Edema

A total of 9 RCTs representing 1880 patients assessed the incidence of peripheral edema within the first 8 to 16 weeks of initiating therapy (Figure 37).[106,183,186,189,190,193,196,197] All nine studies were rated good quality. Meta-analysis by drug class yielded statistically significantly increased odds ratios for phosphodiesterase inhibitors (OR 3.32; 95% CI, 1.40 to 7.87), but the results for endothelin antagonists (OR 1.93; CI, 0.64 to 5.85) and prostanoids (OR 1.85; CI, 0.81 to 4.21) were inconclusive. This finding, however, does not necessarily indicate that phosphodiesterase inhibitors are associated with a higher incidence of peripheral edema relative to endothelin receptor antagonists or prostanoids. There was moderate heterogeneity among the 4 studies of endothelin antagonists, with a Q-value of 7.33 for 3 degrees of freedom, I^2=59.07%, p=0.062.

Three good-quality studies[186,189,193] involving 356 patients evaluated the incidence of peripheral edema associated with combination therapy versus monotherapy. One study evaluated the efficacy of bosentan with epoprostenol as background therapy, one compared sildenafil with placebo with epoprostenol as background therapy, and one evaluated the efficacy of iloprost with bosentan as background therapy. We did not calculate a summary estimate for the odds ratio for peripheral edema associated with combination therapy compared with monotherapy because of the high degree of heterogeneity between studies, including the use of different drugs for both active and background therapy.

Figure 37. Forest plot of effects of therapy by drug class on peripheral edema



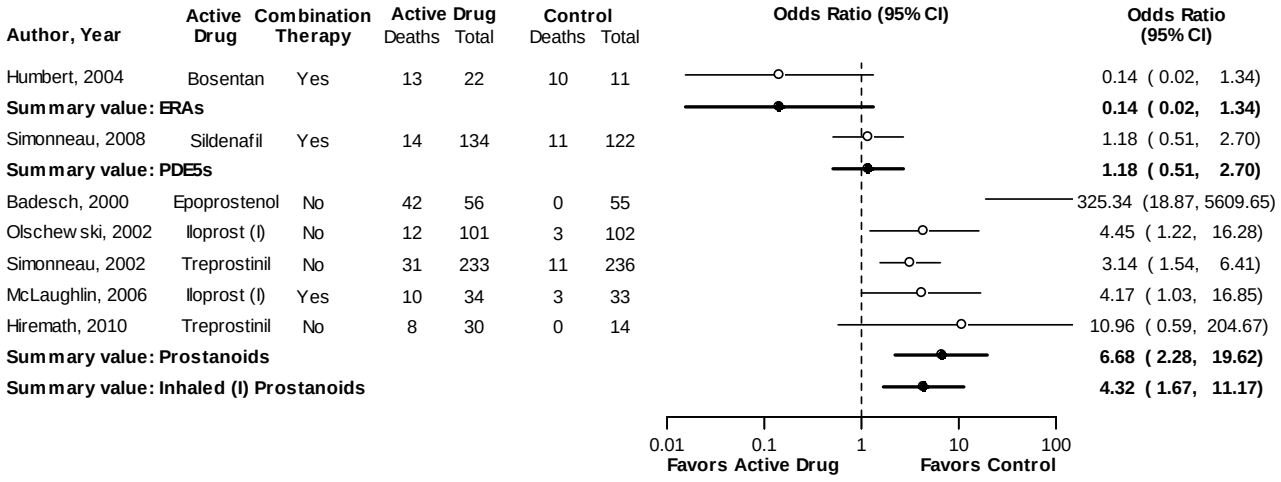
CI = confidence interval; ERA = endothelin receptor antagonist; PDE5 = phosphodiesterase type 5 inhibitor

Jaw Pain

A total of 7 RCTs assessed the incidence of jaw pain within the first 8 to 16 weeks of initiating therapy (Figure 38).[186,189,190,193,194,197,199] Five studies were rated good quality and two fair quality. Of these, 5 RCTs representing 894 patients compared intravenous, subcutaneous, or aerosolized prostanoids with placebo or standard therapy. Meta-analysis of these 5 studies yielded a summary estimate of the odds ratio of 6.68 (95% CI, 2.28 to 19.62). There was moderate heterogeneity among these 5 studies, with a Q-value of 10.01 for 4 degrees of freedom, I^2=60.04%, p=0.04. Aerosolized prostanoids were also associated with a significantly increased risk of jaw pain (OR 4.32; CI, 1.67 to 11.17).

Three good-quality studies[186,189,193] involving 356 patients evaluated the incidence of jaw pain associated with combination therapy versus monotherapy. One study evaluated the efficacy of bosentan with epoprostenol as background therapy, one compared sildenafil with placebo with epoprostenol as background therapy, and one evaluated the efficacy of iloprost with bosentan as background therapy. We did not calculate a summary estimate for the odds ratio for jaw pain associated with combination therapy compared with monotherapy because of the high degree of clinical heterogeneity between studies, including the use of different drugs for both active and background therapy.

Figure 38. Forest plot of effects of therapy by drug class on jaw pain



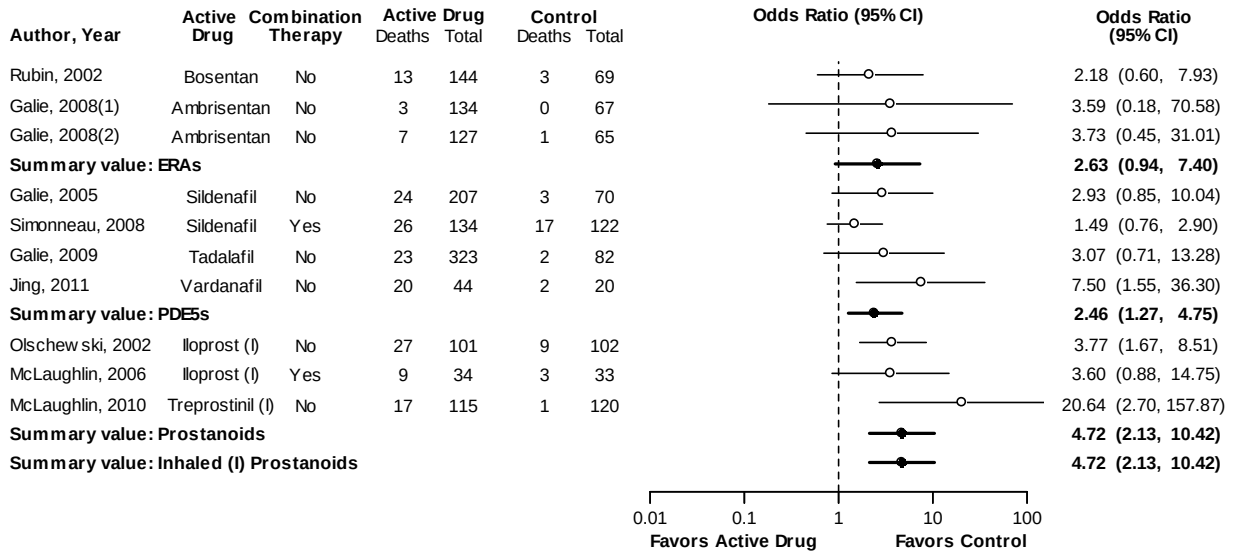
CI = confidence interval; ERA = endothelin receptor antagonist; PDE5 = phosphodiesterase type 5 inhibitor

Flushing

A total of 10 RCTs representing 2113 patients assessed the incidence of flushing within the first 8 to 16 weeks of initiating therapy (Figure 39).[106,131,182,187,189,190,193,196,200] All 10 studies were rated good quality. Meta-analysis of these studies suggest an approximately two-fold increase in the risk of flushing associated with both endothelin antagonists (OR 2.63; 95% CI, 0.94 to 7.40) and phosphodiesterase inhibitors (OR 2.46; CI, 1.27 to 4.75), but the 95-percent confidence interval of the summary estimate for endothelin antagonists includes 1.0. The risk of flushing was also elevated with aerosolized prostanoids (OR 4.72; CI, 2.13 to 10.42). There was moderate heterogeneity among the 4 studies of phosphodiesterase inhibitors, with a Q-value of 4.05 for 3 degrees of freedom, I^2=25.9%, p=0.26.

Two good-quality studies[189,193] involving 323 patients evaluated the incidence of flushing associated with combination therapy versus monotherapy. One study compared sildenafil with placebo with epoprostenol as background therapy and one compared iloprost with placebo with bosentan as background therapy. We did not estimate a summary estimate for the odds ratio for flushing associated with combination therapy compared with monotherapy because of the high degree of clinical heterogeneity between studies, including the use of different drugs for both active and background therapy.

Figure 39. Forest plot of effects of therapy by drug class on flushing



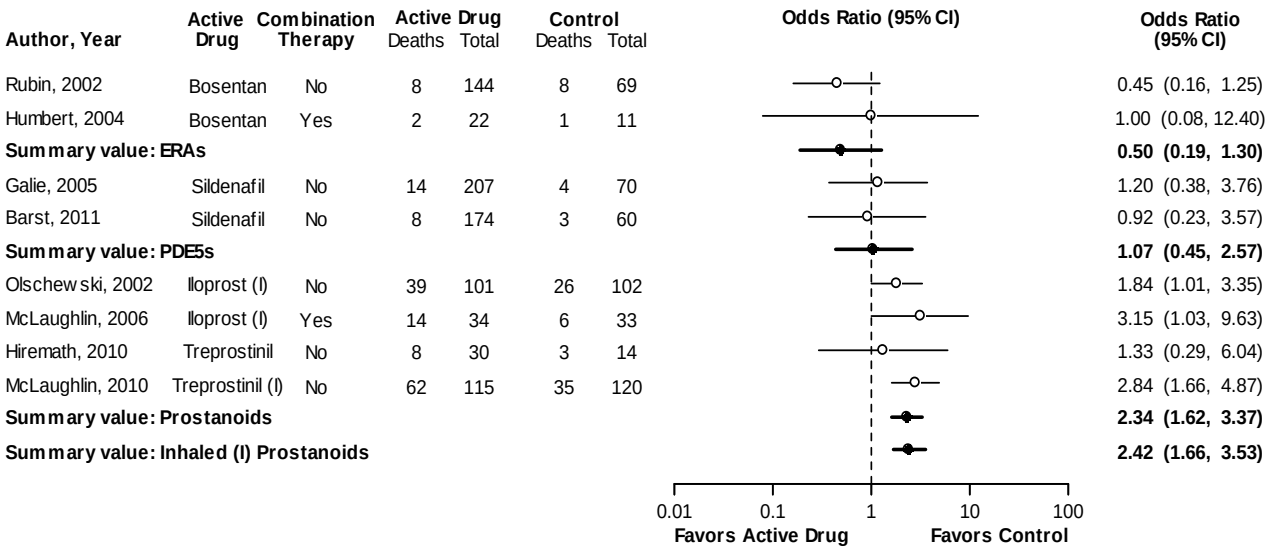
CI = confidence interval; ERA = endothelin receptor antagonist; PDE5 = phosphodiesterase type 5 inhibitor

Cough

A total of 8 RCTs representing 1306 patients assessed the incidence of cough within the first 8 to 16 weeks of initiating therapy (Figure 40).[131,182,186-188,190,193,199] Six studies were rated good quality and two fair quality. There was moderate heterogeneity among the 8 studies, with a Q-value of 12.6 for 7 degrees of freedom, I^2=44%, p=0.08. Meta-analysis of these studies revealed no statistically significant differences in the proportion of patients reporting adverse events between active and control groups for endothelin antagonists and phosphodiesterase inhibitors.

Prostanoids, however, are associated with a higher incidence of cough compared with placebo or standard therapy. The summary estimate of the odds ratio for cough associated with all prostanoids (aerosolized or intravenous) is 2.34 (95% CI, 1.62 to 3.37). There was little evidence of statistical heterogeneity among these 4 studies, with a Q-value of 1.93 for 3 degrees of freedom, I^2=0, p=0.59. Among the 3 studies that used an aerosolized route of administration for prostanoids, the summary estimate of the odds ratio for cough was 2.42 (CI, 1.66 to 3.53). Two good-quality studies[186,193] involving 100 patients evaluated the incidence of cough associated with combination therapy versus monotherapy. One study evaluated the efficacy of bosentan with epoprostenol as background therapy, and one evaluated the efficacy of iloprost with bosentan as background therapy. We did not estimate a summary estimate for the odds ratio for cough associated with combination therapy compared with monotherapy because of the high degree of heterogeneity between studies, including the use of different drugs for both active and background therapy.

Figure 40. Forest plot of effects of therapy by drug class on cough



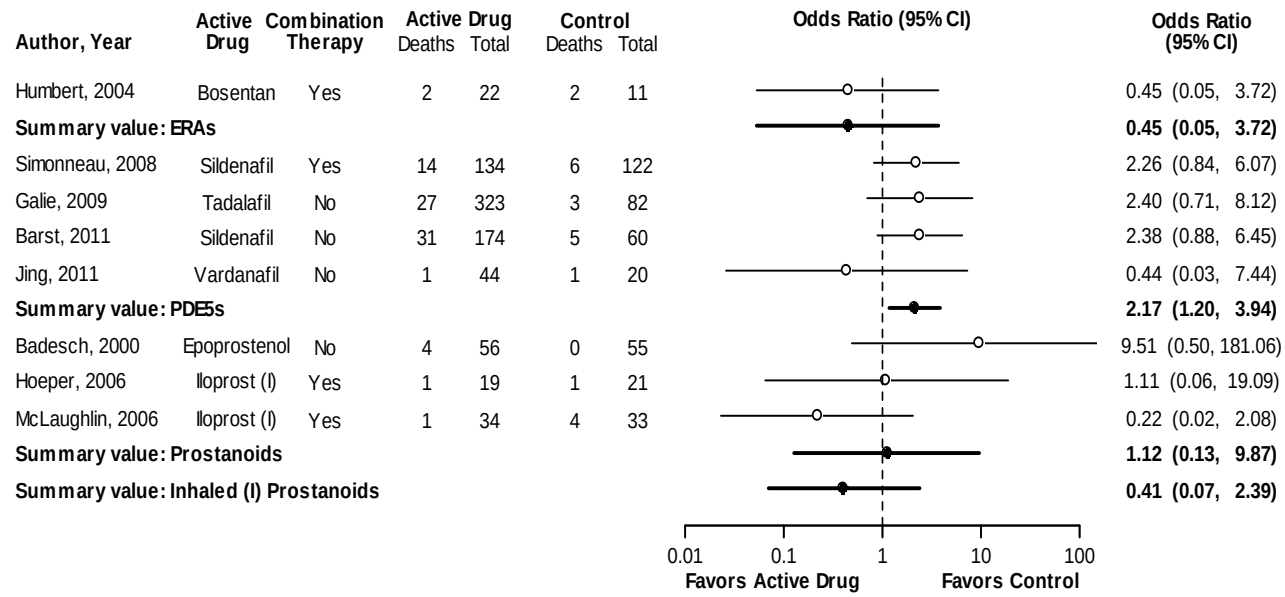
CI = confidence interval; ERA = endothelin receptor antagonist; PDE5 = phosphodiesterase type 5 inhibitor

Infections

A total of 8 RCTs representing 1210 patients assessed the incidence of infections within the first 8 to 16 weeks of initiating therapy (Figure 41).[186,188,189,192-194,196,200] Five studies were rated good quality and three fair quality. There was low heterogeneity among these studies, with a Q-value of 8.0 for 7 degrees of freedom, I^2=12.8%, p=0.33. The single study that compared an endothelin antagonist (bosentan) with placebo with epoprostenol as background therapy did not demonstrate an association between treatment and incidence of infection (OR 0.45; 95% CI, 0.05 to 3.72). Meta-analysis of 4 studies demonstrated an increase in incidence of infections associated with phosphodiesterase inhibitors (OR 2.17; CI, 1.20 to 3.94). There was little evidence of statistical heterogeneity among these 4 studies, with a Q-value of 3.94 for 3 degrees of freedom, I^2=0, p=0.73. Meta-analysis of 3 studies did not demonstrate an association between prostanoid treatment and incidence of infection (OR 1.12; CI, 0.13 to 9.87).

Three good-quality studies[186,189,193] and one fair-quality study[192] involving 396 patients evaluated the incidence of infections associated with combination therapy versus monotherapy. We did not calculate a summary estimate for the odds ratio for infections associated with combination therapy compared with monotherapy because of the high degree of heterogeneity between studies, including the use of different drugs for both active and background therapy.

Figure 41. Forest plot of effects of therapy by drug class on infections



CI = confidence interval; ERA = endothelin receptor antagonist; PDE5 = phosphodiesterase type 5 inhibitor

Summary Strength of Evidence for KQ 3

Results for these outcomes and comparisons, along with ratings for strength of evidence (SOE) are shown in Tables 25–31.

Table 25. Summary strength of evidence for KQ 3: Mortality

Comparison	Number of Studies (Patients)	Domains				Strength of Evidence Effect Estimate (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Ambrisentan vs. placebo	2 (393)	Low (2)	Consistent	Direct	Imprecise	**SOE = Insufficient** OR 0.40 (0.10 to 1.51) Inconclusive benefit (few studies, few deaths lead to wide CI)
Bosentan vs. placebo	3 (411)	Low (2) Moderate (1)	Inconsistent	Direct	Imprecise	**SOE = Insufficient** OR 0.72 (0.14 to 3.60) Inconclusive benefit (few studies, few deaths lead to wide CI)
Epoprostenol vs. placebo or standard therapy	3 (215)	Low (2) Moderate (1)	Inconsistent	Direct	Imprecise	**SOE = Insufficient** OR 0.33 (0.07 to 1.50) Inconclusive benefit (few studies, few deaths lead to wide CI)
Iloprost vs. placebo	2 (266)	Low (1) Moderate (1)	Inconsistent	Direct	Imprecise	**SOE = Insufficient** OR 0.43 (0.08 to 2.47) Inconclusive benefit (few studies, few deaths lead to wide CI)
Sildenafil vs. placebo	1 (277)	Low (1)	NA	Direct	Imprecise	**SOE = Insufficient** OR 1.01 (0.10 to 9.92) Inconclusive benefit (single study, wide CI)

Table 25. Summary strength of evidence for KQ 3: Mortality (continued)

Comparison	Number of Studies (Patients)	Domains				Strength of Evidence Effect Estimate (95% CI)
		Consistency	Directness	Precision	Consistency	
Tadalafil vs. placebo	1 (405)	Low (1)	NA	Direct	Imprecise	**SOE = Insufficient** OR 0.50 (0.05 to 5.63) Inconclusive benefit (single study, wide CI)
Treprostinil vs. placebo	2 (513)	Low (1) Moderate (1)	Consistent	Direct	Imprecise	**SOE = Insufficient** OR 0.50 (0.12 to 2.12) Inconclusive benefit (few studies, few deaths lead to wide CI)
Vardenafil vs. placebo	1 (64)	Low (1)	NA	Direct	Imprecise	**SOE = Insufficient** OR 0.08 (0.00 to 1.82) Inconclusive benefit (single study, wide CI)
Endothelin antagonists vs. placebo	6 (838)	Low (5) Moderate (1)	Inconsistent	Direct	Imprecise	**SOE = Insufficient** OR 0.60 (0.23 to 1.59) Inconclusive benefit (few studies, few deaths lead to wide CI)
Phosphodiesterase inhibitors vs. placebo	4 (1011)	Low (4)	Inconsistent	Direct	Imprecise	**SOE = Insufficient** OR 0.30 (0.08 to 1.11) Inconclusive benefit (few studies, few deaths lead to wide CI)
Prostanoids vs. placebo or standard therapy	8 (1229)	Low (5) Moderate (3)	Inconsistent	Direct	Precise	**SOE = Low** OR 0.52 (0.29 to 0.95) Favors prostanoids
Combination therapy vs. monotherapy	3 (566)	Low (3)	Inconsistent	Indirect	Imprecise	**SOE = Insufficient** OR 0.37 (0.04 to 3.32) Inconclusive benefit (few studies, few deaths lead to wide CI)

CI = confidence interval; NA = not applicable; OR = odds ratio; SOE = strength of evidence

Note: No eligible studies compared tadalafil or vardenafil monotherapy with either placebo or standard therapy.

Table 26. Summary strength of evidence for KQ 3: 6MWD

Comparison	Number of Studies (Patients)	Domains				Strength of Evidence Effect Estimate (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Endothelin antagonists vs. placebo	6 (663)	Low (4) Moderate (2)	Consistent	Direct	Imprecise	**SOE = Moderate** Mean difference 39.9 (21.4 to 58.4) Favors endothelin antagonists
Phosphodiesterase inhibitors vs. placebo	4 (991)	Low (4)	Consistent	Direct	Imprecise	**SOE = Moderate** Mean difference 38.9 (22.0 to 55.9) Favors PDE inhibitors
Prostanoids vs. placebo or standard therapy	7 (933)	Low (4) Moderate (2) High (1)	Consistent	Direct	Imprecise	**SOE = Moderate** Mean difference 27.9 (10.3 to 45.4) Favors prostanoids
Combination therapy vs. monotherapy	3 (363)	Low (2) Moderate (1)	Consistent	Indirect	Imprecise	**SOE = Low** Mean difference 23.9 (8.0 to 39.9) Favors combination therapy

CI = confidence interval; OR = odds ratio; SOE = strength of evidence

Table 27. Summary strength of evidence for KQ 3: Hospitalization

Comparison	Number of Studies (Patients)	Domains				Strength of Evidence Effect Estimate (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Endothelin antagonists vs. placebo	3 (606)	Low (3)	Consistent	Direct	Precise	**SOE = Moderate** OR 0.34 (0.17 to 0.69) Favors endothelin antagonists
Phosphodiesterase inhibitors vs. placebo	4 (1011)	Low (4)	Consistent	Direct	Precise	**SOE = Moderate** OR 0.48 (0.25 to 0.91) Favors PDE inhibitors
Prostanoids vs. placebo or standard therapy	2 (301)	Low (2)	Inconsistent	Direct	Imprecise	**SOE = Insufficient** OR 0.42 (0.06 to 3.08) Inconclusive benefit (few studies, wide CI)
Combination therapy vs. monotherapy	3 (566)	Low (3)	Inconsistent	Indirect	Imprecise	**SOE = Insufficient** OR 0.64 (0.31 to 1.36) Inconclusive benefit (few studies, wide CI)

CI = confidence interval; OR = odds ratio; SOE = strength of evidence

Table 28. Summary strength of evidence for KQ 3: Pulmonary vascular resistance

Comparison	Number of Studies (Patients)	Domains				Strength of Evidence Effect Estimate (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Endothelin antagonists vs. placebo	5 (139)	Low (3) Moderate (2)	Inconsistent	Indirect	Precise	**SOE = Low** Mean difference -217.5 (-424.4 to -10.7) Favors endothelin antagonists
Phosphodiesterase inhibitors vs. placebo	1 (263)	Low (1)	NA	Indirect	Precise	**SOE = Low** Mean difference -224.7 (-339.6 to -109.8) Favors PDE inhibitors
Prostanoids vs. placebo or standard therapy	5 (475)	Low (4) Moderate (1)	Consistent	Indirect	Precise	**SOE = Low** Mean difference -256.2 (-440.4 to -71.9) Favors prostanoids
Combination therapy vs. monotherapy	2 (90)	Low (2)	Inconsistent	Indirect	Imprecise	**SOE = Insufficient** Mean difference -33.2 (-149.5 to 83.1) Inconclusive benefit (few studies, wide CI)

CI = confidence interval; NA = not applicable; OR = odds ratio; SOE = strength of evidence

Table 29. Summary strength of evidence for KQ 3: Mean pulmonary artery pressure

Comparison	Number of Studies (Patients)	Domains				Strength of Evidence Effect Estimate (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Endothelin antagonists vs. placebo	6 (219)	Low (4) Moderate (2)	Consistent	Indirect	Precise	**SOE = Low** Mean difference -3.5 (-6.5 to -0.5) Favors endothelin antagonists
Phosphodiesterase inhibitors vs. placebo	2 (481)	Low (1) Moderate (1)	Consistent	Indirect	Precise	**SOE = Low** Mean difference -3.6 (-5.2 to -2.0) Favors PDE inhibitors
Prostanoids vs. placebo or standard therapy	5 (859)	Low (4) Moderate (1)	Consistent	Indirect	Precise	**SOE = Low** Mean difference -3.2 (-5.6 to -0.8) Favors prostanoids
Combination therapy vs. monotherapy	2 (90)	Low (2)	Inconsistent	Indirect	Precise	**SOE = Low** Mean difference -4.1 (-7.6 to -0.6) Favors combination therapy

CI=confidence interval; OR=odds ratio; SOE=strength of evidence

Table 30. Summary strength of evidence for KQ 3: Cardiac index

Comparison	Number of Studies (Patients)	Domains				Strength of Evidence Effect Estimate (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Endothelin antagonists vs. placebo	2 (63)	Low (2)	Inconsistent	Indirect	Imprecise	**SOE = Insufficient** Mean difference 0.6 (-0.2 to 1.4) Inconclusive benefit (few studies, wide CI)
Phosphodiesterase inhibitors vs. placebo	1 (258)	Low (1)	NA	Indirect	Precise	**SOE = Low** Mean difference 0.3 (0.1 to 0.5) Favors PDE inhibitors
Prostanoids vs. placebo or standard therapy	3 (661)	Low (2) Moderate (1)	Consistent	Indirect	Precise	**SOE = Low** Mean difference 0.4 (0.1 to 0.7)
Combination therapy vs. monotherapy	1 (33)	Low (1)	NA	Indirect	Imprecise	**SOE = Insufficient** Mean difference 0.2 (-0.4 to 0.8) Inconclusive benefit (single study, wide CI)

CI = confidence interval; NA = not applicable; OR = odds ratio; SOE = strength of evidence

Table 31. Summary strength of evidence for KQ 3: Adverse events[a]

Comparison	Number of Studies (Patients)	Domains				Strength of Evidence Effect Estimate (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Endothelin antagonists vs. placebo: Dizziness	3 (300)	Low (3)	Consistent	Direct	Precise	**SOE = Low** OR 0.45 (0.24 to 0.85)
Phospho-diesterase inhibitors vs. placebo: Peripheral edema	2 (661)	Low (2)	Consistent	Direct	Precise	**SOE = Moderate** OR 3.32 (1.40 to 7.87)
Phospho-diesterase inhibitors vs. placebo: Infections	4 (959)	Low (3) Moderate (1)	Inconsistent	Direct	Precise	**SOE = Low** OR 2.17 (1.20 to 3.94)
Phospho-diesterase inhibitors vs. placebo: Headache	5 (1156)	Low (4) Moderate (1)	Consistent	Direct	Precise	**SOE = High** OR 1.98 (1.18 to 3.32) Favors placebo
Phospho-diesterase inhibitors vs. placebo: Flushing	4 (1002)	Low (4)	Consistent	Direct	Precise	**SOE = Moderate** OR 2.46 (1.27 to 4.75) Favors placebo
Prostanoids (aerosolized) vs. placebo: Headache	3 (505)	Low (3)	Consistent	Direct	Precise	**SOE = High** OR 2.35 (1.50 to 3.70)

Table 31. Summary strength of evidence for KQ 3: Adverse events[a] (continued)

Comparison	Number of Studies (Patients)	Domains				Strength of Evidence Effect Estimate (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Prostanoids (aerosolized) vs. placebo: Jaw pain	2 (270)	Low (2)	Consistent	Direct	Precise	**SOE = High** OR 4.32 (1.67 to 11.17) Favors placebo
Prostanoids (aerosolized) vs. placebo or standard therapy: Flushing	3 (505)	Low (3)	Consistent	Direct	Precise	**SOE = Moderate** OR 4.72 (2.13 to 10.42) Favors placebo
Prostanoids (aerosolized) vs. placebo: Cough	3 (505)	Low (3)	Consistent	Direct	Precise	**SOE = High** OR 2.42 (1.66 to 3.53) Favors placebo

CI = confidence interval; OR = odds ratio; SOE = strength of evidence

[a]Only meta-analyses that generated a summary estimate with 95% confidence intervals that did not cross 1.0 or were too imprecise to conclude no difference between groups are included in this table.

Discussion

Key Findings and Strength of Evidence

In this comparative effectiveness review, we included 60 studies involving 7096 patients that evaluated biomarker tests, echocardiography, or both, to screen for PAH (KQ 1); 99 studies involving 8655 patients that evaluated biomarker tests, echocardiography, or both, to diagnose and follow progression of disease as well as response to therapy for PAH (KQ 2); and 37 studies involving 4192 patients that assessed the effectiveness of drug treatments for PAH in adults.

KQ 1: Screening for PAH

We found 1 study involving 372 patients that evaluated the combination of biomarker tests and echocardiography to echocardiography alone to screen for PAH (Key Question [KQ] 1). Based on one good-quality prospective cohort study, biomarker testing with NT-proBNP may be useful in ruling out PAH among those suspected of PH who also have elevated sPAP by echocardiography;[26] however, no data are available regarding combined echocardiography and biomarker screening in asymptomatic patients at high risk for PAH. In the absence of other direct comparative trials, we attempted to address this question by evaluating the efficacy of biomarker and echocardiography independently for screening and diagnosis of PAH. We reviewed 60 studies involving 7096 patients that evaluated biomarker tests, echocardiography, or both, to screen for PAH. The associations between natriuretic peptide testing and PAH diagnosis is insufficiently strong to support its use alone as a screening test in either asymptomatic or symptomatic patients suspected of PAH. Data on biomarker testing were essentially limited to a single test—NT-proBNP—which showed only moderate correlation with RHC hemodynamic measures and showed a great deal of variability between studies in its diagnostic accuracy and discrimination.

We found that echocardiography estimates of pulmonary artery pressures (sPAP, TG, and TRV) and pulmonary vascular resistance (TRV/VTI_{RVOT}) demonstrated good accuracy in screening for PAH. In low prevalence populations (<10%), negative predictive value of a normal sPAP is high, suggesting that echocardiography with a low threshold may be an appropriate test in asymptomatic high-risk populations or in patients with symptoms suggesting PAH. (This is shown in studies of liver transplant studies with complete verification).

Our findings suggest that echocardiographic estimation of sPAP may be sufficiently accurate to justify its role in screening for PAH in symptomatic patients suspected of having PH. However, this conclusion has several important caveats. First, echocardiography in a small, but significant, number of patients may not produce an estimate of sPAP because of poor-quality Doppler visualization of the tricuspid regurgitant jet. Second, echocardiographic estimates of sPAP often over- or under-estimate pulmonary artery pressure enough to result in misclassification according to PAH diagnostic threshold—hence the selection of a test threshold is critical for the aim of screening. A single test threshold is insufficient to perform with simultaneously high sensitivity and specificity (or PPV and NPV), especially in populations with higher risk or higher prevalence (more symptomatic), where echocardiography cannot be relied upon to exclude pulmonary hypertension if pretest probability is high. In asymptomatic patients at high risk for PH, echocardiography seems to perform with similar sensitivity and specificity; however, these studies suffer from verification bias, which likely inflates both the sensitivity and specificity estimates. Two prospective studies that show approximately 10 percent of

asymptomatic patients with systemic sclerosis and normal sPAP develop PH when serially retested with echocardiography are consistent with either misclassification at baseline echocardiographic screening or prospective development of PH. This would suggest that if echocardiographic screening of asymptomatic patients with a high-risk diagnosis were to be undertaken, then serial testing would be necessary.

Table 32 summarizes the findings of our review and the strength of evidence (SOE) for the available outcomes of sensitivity, specificity, correlation coefficients, and adverse effects of biomarker and echocardiographic tests.

Table 32. Summary of strength of evidence and effect estimates for echocardiography vs. echocardiography plus biomarkers as screening modalities for PAH (KQ 1)[a]

Test	Sensitivity	Specificity	Correlation with RHC
Echo sPAP with NT-proBNP versus Echo sPAP in symptomatic patients	SOE = Insufficient (1 study, 121 patients) NT-proBNP >80 pg/mL has a low false negative rate compared with RHC reference standard; the serial testing study design did not allow for NT-proBNP testing to improve sensitivity beyond that of echo sPAP alone	SOE = Low (1 study, 121 patients) NT-proBNP ≤80 pg/mL ruled out PAH in 9–16% of patients with elevated echo sPAP ≥36 mmHg	SOE = Insufficient (No studies)
Echo sPAP with NT-proBNP versus Echo sPAP in asymptomatic patients	SOE = Insufficient (No studies)	SOE = Insufficient (No studies)	SOE = Insufficient (No studies)
NT-proBNP compared with RHC	SOE = Low (3 studies, 198 patients) NT-proBNP has variable sensitivity (range, 56% to 100%) for diagnosing PAH; uncertain performance for ruling out PAH	SOE = Low (3 studies, 198 patients) NT-proBNP has variable specificity (range, 24% to 95%); uncertain performance for ruling in PAH	SOE = Moderate (3 studies, 176 patients) Correlation of NT-proBNP and RHC is only moderate (range, 0.43 to 0.72)
TRV/TG/sPAP compared with RHC	SOE = Moderate (19 studies, 2459 patients) Echocardiographic estimate of sPAP showed variable sensitivity ranging from 58% to 100%, with lower prevalence studies finding higher sensitivity	SOE = Moderate (19 studies, 2459 patients) Echocardiographic estimate of sPAP showed variable specificity ranging from 50% to 98%, with lower prevalence studies finding higher specificity	SOE = Moderate (23 studies, 4217 patients) Echocardiographic estimates of sPAP showed moderate to strong correlation (range, 0.38 to 0.96) with RHC and were on average unbiased, but were limited by imprecision and by a significant minority of patients in whom TRV was not measurable

Table 32. Summary of strength of evidence and effect estimates for echocardiography vs. echocardiography plus biomarkers as screening modalities for PAH (KQ 1)[a] (continued)

Test	Sensitivity	Specificity	Correlation with RHC
TRV/VTI$_{RVOT}$ compared with RHC	SOE = Moderate (6 studies, 196 patients) Echocardiographic estimate of PVR showed reasonably high sensitivity (range, 89% to 100%) for ruling in PAH	SOE = Moderate (6 studies, 196 patients) Echocardiographic estimate of PVR showed variable specificity (range, 50% to 97%), with better specificity in lower prevalence studies (range, 94% to 97%)	SOE = High (6 studies, 196 patients) Strong correlation between echocardiographic estimates of PVR and PVR by RHC (range, 0.74 to 0.84)

NT-proBNP = N-terminal pro-B-type natriuretic peptide; RHC = right heart catheterization; SOE = strength of evidence; sPAP = systolic pulmonary artery pressure; TRV = tricuspid regurgitant jet velocity; VTI$_{RVOT}$ = velocity-time integral of right ventricular outflow tract

[a]Gray background indicates insufficient SOE.

KQ 2: Management of PAH

Currently, right heart catheterization (RHC) is the reference standard for diagnosing and monitoring progression of PAH. Several biomarkers and echocardiographic parameters have been proposed as potential alternatives to frequent RHC monitoring. In KQ 2 we reviewed studies that evaluated the most commonly studied biomarkers (natriuretic peptides, endothelin-1, uric acid, troponin T, nitric oxide, asymmetric dimethylarginine, cyclic guanosine monophosphate, and D-dimer) and echocardiographic parameters (RV size, RA size, FAC, TAPSE, RIMP/MPI/Tei index, sPAP, mPAP, TR jet, peak TR jet, RVOT, RVEF, RVSP or pericardial effusion) to determine the ability of these measures to assess severity of disease, predict mortality or lung transplantation, or assess response to therapy.

In studies evaluating correlation of the above measures with RHC measures or a commonly used measure of disease severity (6MWD) studies were too underpowered to give reliable results. However, by combining studies looking at the same parameters and performing a meta-analysis we were able to increase the power for seven different comparisons: (1) BNP versus RHC-mPAP, (2) BNP versus RHC-PVR, (3) BNP versus RHC-CI, (4) BNP versus RHC-RAP, (5) BNP versus RHC-PCWP, (6) BNP versus 6MWD, and (7) echocardiography-derived sPAP versus RHC-sPAP. BNP showed only moderate correlation with most RHC measures (mPAP, PVR, cardiac index, RAP) and clinical measures of disease severity (6MWD) and showed weak correlation with PCWP. Most effect estimates were precise (mPAP, PVR, CI, RAP, 6MWD), but estimates for PCWP were imprecise, making it difficult to interpret the clinical importance of the findings for this measure. For the other measures, correlation with BNP was moderate, indicating that BNP levels alone could not serve as an accurate surrogate marker for disease severity. Echocardiography-derived sPAP showed strong correlation with RHC-sPAP, although there was a great deal of heterogeneity among these studies and only moderate strength of evidence to support the use of this measure.

In studies evaluating the ability of biomarkers or echocardiographic measures to predict mortality, we were able to perform a meta-analysis on six measures: BNP, pericardial effusion, RA size, FAC, uric acid and TAPSE. BNP level and pericardial effusion were strong predictors of mortality. RA size was also predictive of mortality. Data on uric acid suggested an association with mortality, while fractional area change (FAC) showed uncertain association with mortality.

The remaining studies that were not included in the meta-analyses were considered to provide insufficient evidence due to small size and poor quality.

Several studies evaluated mean or median levels of biomarkers or echocardiographic parameters at various points in time or as a change from baseline to evaluate response to therapy. Due to the small number and heterogeneity of these studies, we were unable to perform meta-analysis on these data. While a few studies found changes in biomarkers or echocardiographic parameters in response to various treatments, there were insufficient data to quantitatively assess overall response or to recommend use of these markers as surrogate outcomes measures.

We found no studies addressing diagnostic thinking efficacy, therapeutic efficacy, or safety concerns with echocardiography or biomarkers.

The strength of evidence (SOE) ratings for the most commonly reported biomarkers and echocardiographic parameters are summarized in Table 33 (management of PAH) and Table 34 (prediction of patient outcomes).

Table 33. Summary of strength of evidence and effect estimates for the use of echocardiography or biomarkers in the management of PAH (KQ 2)

Comparison	Number of Studies (Patients)	Summary Correlation Coefficient Estimate (95% CI)	SOE and Findings
BNP compared with RHC-mPAP	14 (606)	0.39 (0.31 to 0.47)	SOE = Moderate Serum BNP level shows moderate correlation with mPAP
BNP compared with RHC-PVR	13 (684)	0.46 (0.31 to 0.59)	SOE = Low Serum BNP level shows moderate correlation with PVR
BNP compared with RHC-RAP	12 (645)	0.47 (0.40 to 0.54)	SOE = Moderate Serum BNP level shows moderate correlation with RAP
BNP compared with RHC-CI	10 (550)	-0.42 (-0.54 to -0.28)	SOE = Low Serum BNP level shows negative moderate correlation with cardiac index
BNP compared with PCWP	5 (319)	0.16 (0.01 to 0.31)	SOE = Low Serum BNP level shows poor correlation with PCWP
BNP compared with 6MWD (absolute)	9 (484)	-0.46 (-0.55 to -0.35)	SOE = Moderate Serum BNP level shows negative moderate correlation with 6MWD
Echocardiography-derived sPAP compared with RHC-sPAP	9 (362)	0.76 (0.53 to 0.89)	SOE = Low sPAP estimated by echocardiography shows good correlation with sPAP from RHC

6MWD = 6-minute walk distance; BNP = B-type natriuretic peptide; CI = confidence interval; FAC = fractional area change; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; RA = right atrium; RAP = right atrial pressure; RHC = right heart catheterization; SOE = strength of evidence; sPAP = systolic pulmonary artery pressure

Table 34. Summary of strength of evidence and effect estimates for the use of echocardiography or biomarkers in the prediction of mortality (KQ 2)[a]

Marker	Number of Studies (Patients)	Summary Hazard Ratio Estimate (95% CI)	SOE and Findings
BNP	6 (407)	2.42 (1.72 to 3.41)	SOE = Moderate Increase in log-transformed BNP level is a good predictor of mortality
Pericardial effusion	8 (2590)	2.43 (1.57 to 3.77)	SOE = Moderate Presence of pericardial effusion is a strong predictor of mortality, although there was wide variability in results for this measure
RA size	4 (242)	1.06 (1.01 to 1.10)	SOE = Moderate RA size is a predictor of mortality
FAC	4 (242)	0.98 (0.96 to 1.01)	SOE = Moderate FAC is a poor predictor of mortality
Uric acid	4 (246)	1.01 (1.00 to 1.01)	SOE = Low Small increase in mortality but imprecision of estimates limit these data
TAPSE	4 (251)	0.94 (0.82 to 1.08)	SOE = Insufficient Inconsistent results between studies lead to uncertainty

BNP = B-type natriuretic peptide; CI = confidence interval; FAC = fractional area change; RA=right atrium; RAP = right atrial pressure; SOE = strength of evidence

[a]Gray background indicates insufficient SOE.

KQ 3: Pharmacotherapy for PAH

The treatment options for PAH currently are based on three main classes of drugs: endothelin receptor antagonists (ambrisentan, bosentan); phosphodiesterase-5 inhibitors (sildenafil, tadalafil); and prostacyclin-analogues (epoprostenol, iloprost, treprostinil). Few RCTs have been performed to date to fully evaluate the efficacy of these drugs—individually or in combination.

We reviewed 28 RCTs studies involving 3613 patients and 9 nonrandomized observational studies involving 579 patients that assessed the effectiveness of drug treatment for PAH in adults. Our review found inconclusive evidence regarding mortality reduction for 11 of the 12 drug treatment comparisons:

- Ambrisentan versus placebo (OR 0.40; 95% CI, 0.10 to 1.51)
- Bosentan versus placebo (OR 0.72; CI, 0.14 to 3.60)
- Epoprostenol versus placebo or standard therapy (OR 0.33; CI, 0.07 to 1.50)
- Iloprost versus placebo (OR 0.43; CI, 0.08 to 2.47)
- Sildenafil versus placebo (OR 1.01; CI, 0.10 to 9.92)
- Tadalafil versus placebo (OR 0.50; CI, 0.05 to 5.63)
- Treprostinil versus placebo (OR 0.50; CI, 0.12 to 2.12)
- Vardenafil versus placebo (OR 0.08; CI, 0.00 to 1.82)
- Endothelin antagonists versus placebo (OR 0.60; CI, 0.23 to 1.59)

- Phosphodiesterase inhibitors versus placebo (OR 0.30; CI, 0.08 to 1.11)
- Combination therapy versus monotherapy (OR 0.37; CI, 0.04 to 3.32)

However, for prostanoids versus placebo or standard therapy, there was a statistically significant improvement in mortality (OR 0.52; CI, 0.29 to 0.95, low strength of evidence). Few deaths were observed in these limited-duration studies, leading to wide confidence intervals and lack of statistical power to detect a difference; however, a consistent direction of effect and demonstrated improvements in other outcomes, including functional and hemodynamic measures, support that a mortality reduction might exist.

The combination therapy analyzed included three different combinations of drugs: sildenafil plus IV epoprostenol versus IV epoprostenol plus placebo; bosentan plus IV epoprostenol versus IV epoprostenol plus placebo; and bosentan or sildenafil plus inhaled treprostinil versus bosentan or sildenafil plus placebo. Our results are similar to a recent meta-analysis by Fox et al.,[210] which found no significant change in mortality with combination therapy compared with monotherapy for PAH (OR 0.42; 95% CI, 0.08 to 2.26). Clearly more studies are needed in this area.

In studies evaluating 6MWD, we performed four meta-analyses: (1) endothelin receptor antagonists versus placebo, (2) phosphodiesterase-5 inhibitors versus placebo, (3) prostanoids versus placebo or standard therapy, and (4) combination therapy versus monotherapy. Increases in 6MWD ranging from 27.9 meters (95% CI, 10.3 to 45.4) to 39.9 meters (CI, 21.4 to 58.4) were observed in trials of all drug classes when compared with placebo or standard therapy; however, comparisons between agents are inconclusive. The magnitude of these statistically significant improvements in 6MWD associated with treatment are very close to a recently published estimate of 33 meters for the minimal important difference for the 6MWD in patients with PAH.[211] Combination therapy also showed improved 6MWD compared with monotherapy (OR 23.9; CI, 8.0 to 39.9), but the diversity of treatment regimens and the small number of combination therapy trials again make comparisons between specific regimens inconclusive.

In studies evaluating hospitalization, we performed four meta-analyses: (1) endothelin receptor antagonists versus placebo, (2) phosphodiasterase-5 inhibitors versus placebo, (3) prostanoids versus placebo, and (4) combination therapy versus monotherapy. In patients taking the endothelin receptor antagonists and phosphodiesterase-5 inhibitors, the odds ratio of hospitalization was lower compared with placebo (OR 0.34 and 0.48, respectively). The magnitude of the odds ratio associated with prostanoids was similar (OR 0.42), but the 95% confidence interval included 1.0, thereby making this finding not statistically significant and inconclusive. Combination therapy compared with monotherapy also showed a similar nonsignificant effect on hospitalization (OR 0.64).

In studies using right heart catheterization to follow response to therapy, we performed meta-analyses on the following outcomes: (1) pulmonary vascular resistance, (2) mean pulmonary artery pressure, and (3) cardiac index. We found modest improvements in all three measures associated with phosphodiesterase inhibitors and prostanoids and improvements in two measures (mPAP and cardiac index) associated with endothelin antagonists. The clinical significance of the magnitude of the observed changes is unclear. Meta-analysis of two studies that compared combination therapy with monotherapy revealed a modest but statistically significant improvement in mPAP associated with combination therapy and insufficient evidence for PVR and cardiac index.

In studies reporting adverse effects, we found that phosphodiesterase-5 inhibitors were more likely to cause headache than endothelin receptor antagonists were, and endothelin antagonists still were more likely to cause headache than placebo. Drugs did not significantly differ in their

odds of causing dizziness or diarrhea. Aerosolized prostanoids were much more likely to cause jaw pain and cough compared with placebo. Phosphodiesterase-5 inhibitors and prostanoids were associated with flushing, while data on endothelin receptor antagonists were inconclusive. Phosphodiesterase-5 inhibitors had a significant association with peripheral edema while data on prostanoids and endothelin receptor antagonists were inconclusive.

The strength of evidence (SOE) ratings are summarized in Table 35.

Table 35. Summary of strength of evidence and effect estimates for monotherapy versus combination therapy for PAH (KQ 3)[a]

Intervention	Mortality	6MWD (m)	Hospitalization
Endothelin antagonist vs. placebo	SOE = Insufficient (6 studies, 838 patients) Inconclusive benefit (few studies, few deaths lead to wide CI) OR 0.60 (95% CI, 0.23 to 1.59)	SOE = Moderate (6 studies, 663 patients) Improved 6MWD with endothelin antagonists compared with placebo Mean difference 39.9 (95% CI, 21.4 to 58.4)	SOE = Moderate (3 studies, 606 patients) Reduced risk of hospitalization OR 0.34 (95% CI, 0.17 to 0.69)
Phosphodiesterase inhibitors vs. placebo	SOE = Insufficient (4 studies, 1,011 patients) Inconclusive benefit (few studies, few deaths lead to wide CI) OR 0.30 (95% CI, 0.08 to 1.11)	SOE = Moderate (4 studies, 991 patients) Improved 6MWD with PDE5 therapy compared with placebo or standard therapy Mean difference 38.9 (95% CI, 22.0 to 55.9)	SOE = Moderate (4 studies, 1,011 patients) Reduced risk of hospitalization OR 0.48 (95% CI, 0.25 to 0.91)
Prostanoids vs. placebo or standard therapy	SOE = Low (8 studies, 1,229 patients) Lower mortality with prostanoids, but inconsistent results and wide CI OR 0.52 (95% CI, 0.29 to 0.95)	SOE = Moderate (7 studies, 933 patients) Improved 6MWD with prostanoid therapy compared with placebo Mean difference 27.9 (95% CI, 10.3 to 45.4)	SOE = Insufficient (2 studies, 301 patients) Inconclusive benefit (few studies, wide CI) OR 0.42 (95% CI, 0.06 to 3.08)
Combination vs. monotherapy	SOE = Insufficient (3 studies, 566 patients) Inconclusive benefit (few studies, few deaths lead to wide CI) OR 0.37 (95% CI, 0.04 to 3.32)	SOE = Low (3 studies, 363 patients) Improved 6MWD with combination therapy compared with monotherapy Mean difference 23.9 (95% CI, 8.0 to 39.9)	SOE = Insufficient (3 studies, 566 patients) Inconclusive benefit (few studies, wide CI) OR 0.64 (95% CI, 0.31 to 1.36)

6MWD = 6-minute walk distance; CI = confidence interval; NS = not statistically significant; OR = odds ratio; SOE=strength of evidence

[a]Gray background indicates insufficient SOE.

Findings in Relation to What is Already Known

Two previous meta-analyses of echocardiography for diagnosing pulmonary hypertension, focusing solely on sPAP, drew similar conclusions to our review, despite methodological

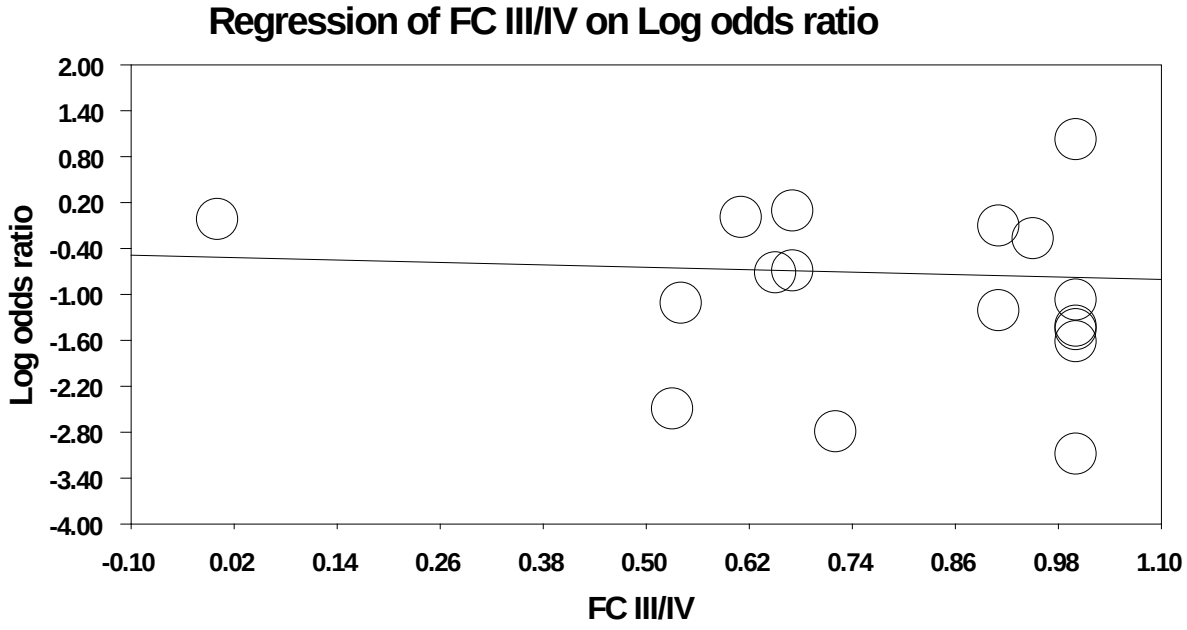
differences, suggesting that our findings are robust. Zhang et al.[212] analyzed six studies, finding a summary sensitivity of 0.82 (95% CI; 0.76 to 0.88) and summary specificity of 0.68 (95% CI, 0.64 to 0.72). These estimates are somewhat lower that our findings. Despite inclusion criteria that seem to be similar, Zhang et al.[212] included fewer eligible studies than our review even taking into account the date range. Another more recent analysis that included more studies had broader inclusion criteria including patients with COPD and heart failure who were not suspected of having PAH.[213] Summary estimates of sensitivity of 0.83 (CI, 0.73 to 0.90) and specificity of 0.72 (CI, 0.53 to 0.85) were closer to our findings. This study found significant heterogeneity and, given larger numbers of included studies, was able to undertake various sensitivity analyses to explore the reasons for heterogeneity; however, none of the characteristics examined—including prospective studies, study year, population (cardiac versus lung), interval between echocardiography and RHC, and method of RAP estimate—revealed a source for the heterogeneity. Both reviews concluded that echocardiography has acceptable accuracy for use as the initial measure of pulmonary pressures in evaluating patients in whom PH is suspected, but not sufficient accuracy to diagnose PH without RHC.

KQ 2 focused on determining whether echocardiographic parameters and/or biomarkers have value in the management of PAH. The current guidelines for diagnosis and treatment of pulmonary hypertension have identified the presence of pericardial effusion, indexed right atrial area, LV eccentricity index, and RV Doppler index (RIMP/MPI/Tei index) as the echocardiographic parameters having the best prognostic value. TAPSE has also been reported to have some prognostic value.[12] Our findings confirm that pericardial effusion and right atrial size were strong predictors of mortality; however, we found TAPSE did not predict mortality, and we had insufficient data to evaluate the prognostic value of LV eccentricity index or RV Doppler index. These guidelines have also reported that uric acid, ANP, BNP, and troponin T have prognostic value in PAH. In our review, BNP level was associated with mortality and also showed moderate correlation with hemodynamic measures such as RAP and PVR as well as clinical outcomes such as the 6MWD, which have all been reported by the current guidelines to be strong predictors of prognosis. Prior studies also have attempted to determine an optimal cutoff point for BNP levels to most accurately predict prognosis, but we had insufficient data to make any such determination. We also had insufficient data to determine the prognostic significance of other biomarkers. We did find that echocardiography-derived sPAP correlated strongly with RHC-sPAP, but given that sPAP is considered less important than mPAP in terms of prognostic value for PAH, this correlation may be of limited clinical utility.

For KQ 3, our results are similar to a recent meta-analysis by Fox et al.,[210] which found no significant change in mortality with combination therapy compared with monotherapy for PAH (RRR 0.42; 95% CI, 0.08 to 2.26). Our assessment resulted in minor differences that did not impact the conclusions of the study, including a reversal of the effect direction in one study of 6MWD[192] and inability to reproduce the mortality data from another study.[209] Our findings are consistent with those of another meta-analysis of similar scope that also reported a significant effect of prostanoids on mortality.[214]

Another finding from Fox et al. suggested a relationship between the efficacy of treatment on mortality and functional class severity in individual trials. A meta-regression showed greater reduction in mortality in trials with higher proportions of functional class III or IV patients (R^2=0.51). We reexamined this hypothesis in our set of data, which included several more trials with lower proportions of functional class III or IV patients. We found no significant association (p=0.82) (Figure 42).

Figure 42. Regression of functional class on log odds ratio



Applicability

The principal limitations to applicability of data on the diagnosis of PAH all relate to the patient populations studied. First, the studies may not be applicable to the screening of asymptomatic patients. None of the study populations consisted entirely of asymptomatic patients and, although many studies included some patients without symptoms, they were not reported separately in terms of outcomes. Some studies of populations in whom PAH was suspected failed to adequately describe the basis for a clinical suspicion of PAH, whether symptoms of dyspnea, clinical signs, or other test results, such as diffusion capacity of the lung for carbon monoxide (DLCO), thus also limiting the applicability of these studies for screening symptomatic patients. Second, the spectrum of disease among study populations was often skewed, particularly in case-control studies, by selection criteria that selected from patients with known PAH (cases) and patients known not to have PAH (controls). Such studies usually excluded participants with other conditions that might be confused with PAH such as PH due to left-sided heart failure, thrombotic disease, or chronic obstructive pulmonary disease. Third, participants in many studies had a wide range of disease severity, particularly those cases in case-control design studies, which is a poor match for the question at hand. Other applicability issues identified in the KQ 1 studies were less frequent and judged to be less severe.

Our findings in KQ 2 assessing the prognostic or predictive value of biomarkers and echocardiography may not be applicable to all PAH populations. The greatest concern is that studies in KQ 2 included participants at widely differing points in the natural history of disease, who had widely differing degrees of disease severity and different underlying etiologies of PAH. There was also concern that the population was not adequately described to assess applicability, included patients with conditions other than PAH, or in general did not match the review question. Applicability may also be limited by the use of surrogate markers that may not be clinically relevant and insufficient followup time. In a few studies, it was also felt that the

intervention arm or cointerventions did not adequately reflect current clinical practice or that the study setting was widely divergent from the current typical U.S. setting. Finally, there is concern that some studies did not provide adequate information about adverse events.

Applicability considerations were somewhat different for KQ 3 than for the Key Questions about screening and management of PAH. Most of the studies included in this review for KQ 3 were RCTs with generally good internal validity. Patient populations, however, differed between studies; variation in eligibility criteria resulted in differences between study populations in severity of illness, underlying etiology of PAH, comorbid conditions, and prior and concurrent treatment. Many different countries were represented, thereby introducing potential differences in clinical practice and care delivery settings relative to current practice in typical settings the U.S. There was also concern that the population was not always adequately described to assess applicability, with few studies exploring potential differences in response to treatment among different patient subgroups.

Implications for Clinical and Policy Decisionmaking

With regard to screening for PH with echocardiography, our findings are generally consistent with the approach used in the guidelines from the European Society of Cardiology (ESC)/European Respiratory Society (ERS),[12,215] which describe a stratification based on echocardiographic TRV or sPAP and other echocardiographic variables suggestive of pulmonary hypertension (PH):

- PH unlikely: TRV ≤2.8 m/s or sPAP ≤36 mmHg and no additional echocardiographic variable suggestive of PH
- PH possible: TRV ≤2.8 m/s or sPAP ≤36 mmHg but with additional echocardiographic variable suggestive of PH or TRV 2.9–3.4 m/s or sPAP 37–50 mmHg
- PH likely: TRV >3.4 m/s or sPAP >50 mmHg

The additional echocardiographic variables include increased velocity of pulmonary valve regurgitation and a short acceleration time of RV ejection into the PA. The guideline noted that RA and RV dilation, abnormal septum shape or function, increased RV wall thickness, and dilated main PA occur late in the course of PH and thus have questionable value in screening.

The guideline specifically recommends against screening to identify mild, asymptomatic PH because of the high frequency of both underestimation and overestimation of pulmonary artery pressures by echocardiography. Hence, the thresholds are set high. This guideline recommends that echocardiography always be performed when PH is suspected. Also recommended is echocardiographic screening of patients who are candidates for liver transplantation and symptomatic patients with liver disease, connective tissue diseases, HIV infection, and lung disease. The only suggestion for screening asymptomatic patients is for patients with the scleroderma spectrum of diseases, in whom screening "may be considered." The lack of direct comparisons between assessment strategies, and the lack of measures of clinical outcomes associated with screening diagnostic or prognostic testing, would not seem to support more directive recommendations regarding testing modalities.

Our findings support using echocardiography or biomarkers to assess disease severity, prognosis, or response to therapy. Echocardiography-derived sPAP shows promise as a possible surrogate marker for RHC-sPAP, but whether or not this measure alone is adequate to assess disease severity, prognosis, or response to therapy is unclear, and so this evidence is insufficient to support recommendations regarding policy changes.

The findings from our meta-analyses of the few studies that compared combination therapy with monotherapy suggest, but do not prove, that combination therapy confers more benefit than does monotherapy in the treatment of PAH. These findings are generally consistent with the ESC/ERS guideline recommendation for monotherapy as initial treatment, with combination treatment reserved for patients who have an inadequate clinical response to monotherapy.[12,215]

Limitations of the Comparative Effectiveness Review Process

The process of a comparative effectiveness review calls for specifying the scope and methods a priori. In this review, certain decisions made in designing the review resulted in limitations to this report. First, although we did not intend to exclude studies of children, some of the inclusion criteria we established had the effect of eliminating much of the literature on children with PAH. These criteria included the requirement for RHC verification of diagnoses of PAH and, for therapy trials, a minimum followup of 3 months. Studies in children, particularly newborns with PPHN, often omitted RHC and reported outcomes in shorter followup intervals. Second, we anticipated better quality data for the questions about screening and diagnosis (KQ 1) and prognosis (KQ 2) than we actually found.

For KQ 3, certain limitations existed in our search criteria, which may have limited the analysis. First, as with all meta-analyses, there is the potential for bias due to analyzing published studies, which are more likely to have positive results. We investigated this possibility by creating a funnel plot that included 17 of the 28 RCTs that met eligibility criteria for KQ 3 and that reported 6MWD as an outcome at 8 to 16 weeks after randomization to treatment. Visual inspection of the funnel plot suggests an absence of publication bias. We selected studies that reported 6MWD for this assessment of possible publication bias because this is the major outcome that was most commonly reported, and because there were too few studies that consistently reported other outcomes to reliably assess for possible publication bias. Another limitation is that we pooled the lower doses of drug with the higher doses, thereby possibly diluting any treatment effects—either beneficial or harmful—seen in the higher doses. We also may have missed lower doses that were less efficacious. Our analysis of the 6MWD outcome was also hindered by the heterogeneity in the ways studies were reported (mean versus median, and standard deviation versus standard error); we addressed this by converting medians to means and interquartile ranges to standard errors, but this required us to make assumptions about normal distribution of data.

Limitations of the Evidence Base

Current evidence has several important limitations that preclude a firm conclusion about the effectiveness of echocardiography and biomarker screening for PAH. First, studies have most often assembled populations that reflect referral-filter bias and which inadequately document the presence of symptoms and signs related to PAH or to an alternative diagnosis such as congestive heart failure (CHF) or pulmonary fibrosis, etc. In such studies, we found that the diagnostic performance of echocardiographic testing varied with PAH prevalence such that higher prevalence was associated with poorer diagnostic performance. We believe this is related to a higher proportion of conditions that may be confused with PAH and which use screening tests that fail to distinguish these conditions (e.g., PCWP >15 mmHg can be easily found at RHC but is difficult to ascertain by echocardiography; BNP can be similarly elevated in CHF and PAH).

Second, the diagnosis of PAH is based on multiple components that include not only pulmonary artery pressure but also the absence of elevated PCWP and elevated PVR. However, nearly all studies of echocardiographic screening relied on the measurement of a single parameter—TRV—as the sole basis for calculation of TG. TG is the principal component for estimation of sPAP and is a key part of estimation of PVR as TRV/VTI_{RVOT}. In theory, the use of ancillary data of a different sort, such as NT-proBNP, is potentially valuable as a diagnostic strategy.

One study that used serial application of echocardiography and biomarker testing (NT-proBNP) suggests that a combination of echocardiography and biomarker testing can work. With a goal of identifying patients with elevated echocardiography sPAP who could safely refrain from RHC, this study applied a low (highly sensitive) threshold for NT-proBNP and also used ECG evidence of RVH. However, this study was small and, like all of the other studies we identified, suffers from inadequate verification of disease status of at least some screening of test-negative patients.

Given the invasive nature of the RHC reference standard test, it is not surprising that many studies, especially those in lower risk screening populations, would shun widespread verification of test-negative patients. However, the selection of test-negative patients for verification when based on other clinical characteristics (such as DLCO measures or symptoms of dyspnea) was often inadequately reported to quantify the bias due to inadequate verification. None of the studies used an alternate reference standard for test-negative patients; however, two studies that sought to prospectively identify predictors of incident PAH provide valuable insight into this problem—suggesting that approximately 10 percent of echocardiography-screened negative SSc patients would meet PAH diagnostic criteria within 6 to 36 months.

The value of a screening test for early diagnosis depends not only on the diagnostic accuracy of the test for diagnosing the target condition but also the consequences of the different outcomes of testing. These consequences include (1) adverse effects of followup testing or treatment of patients with a false-positive screen and (2) outcomes for patients who go undiagnosed or untreated after a false-negative screen balanced against the benefits that accrue to patients with the target condition who may begin treatment earlier as a result of a true-positive screen. In the case of PAH, although we found no indication of harms related to the screening tests themselves, neither did we find information about the harms of subsequent diagnostic evaluation (such as RHC). Also, there are no clear data on benefits of early treatment or harms from delaying treatment. Thus the considerations are limited to the diagnostic accuracy of testing rather than a broader examination of a policy of screening for early identification.

The main focus of KQ 2 was to determine the comparative effectiveness of biomarkers, echocardiographic parameters, or the combination of both to manage PAH and affect diagnostic thinking efficacy, therapeutic efficacy, and patient outcome efficacy. None of the included studies addressed diagnostic thinking efficacy or therapeutic efficacy. Several studies evaluated changes in levels of biomarkers or echocardiographic parameters in response to therapy, but there were too few studies for any particular marker, as well as significant heterogeneity among studies, leading to insufficient evidence to assess patient outcome efficacy. In addition, no studies evaluated the combination of biomarkers and echocardiography in regard to management of PAH. While there were several studies included in the review that evaluated biomarkers, only BNP had a sufficient number of studies to allow meta-analysis. We limited the evaluation of biomarkers and echocardiographic parameters to those most widely studied; however, the literature review did reveal a wide range of other biomarkers and echocardiographic parameters

in a limited number of studies that may be promising in the management of PAH. Further, while studies evaluating echocardiography or using RHC as a comparator reported results for multiple different parameters, it was unclear in the literature which parameters were most clinically relevant.

Assessing the prognostic value of biomarkers or echocardiographic parameters for such outcomes as the need for transplantation may be biased since all these studies were observational and lacked blinding, and the predictors may have influenced clinical decisions about management or referral for transplantation. Additional research is needed to more fully address the questions posed by KQ 2. Future studies need to evaluate how biomarkers or echocardiography affect diagnostic thinking efficacy and therapeutic efficacy. It has been proposed that a measure that combines a biomarker or biomarkers and echocardiography may be a more effective tool in managing PAH, but research is needed to support this theory. More research needs to be done focusing on response to therapy with increased standardization of duration of followup and medication regimens. A greater body of evidence is needed for novel biomarkers and echocardiographic parameters to effectively assess their usefulness in managing PAH. Future studies should focus on echocardiographic parameters and RHC parameters that are most clinically important.

The evidence for KQ 3 had several limitations. First, we found only a small number of RCTs to analyze. This greatly limited our ability to perform the wide range of meta-analyses on which we had planned, and as such there are gaps in the data. We did not identify any eligible studies that evaluated the comparative effectiveness of calcium channel blockers on intermediate-term and long-term patient outcomes, or that randomized treatment- naïve patients to monotherapy versus combination therapy, or that directly compared two drug classes.

Study populations also were not comparable from study to study, in part because sicker patients are more likely to be receiving prostanoid therapy, so the data on the efficacy of oral therapies may appear to be more favorable because they were studied in patients who were less sick. There is also a paucity of evidence in the published literature to help interpret the clinical significance of the magnitude of effects observed for most outcomes. Recent data on 6MWD, the most commonly assessed outcome measure in the studies analyzed for KQ 3 illustrate this issue. Mathai et al.[211] recently estimated the minimal important difference of the 6MWD for patients with PAH to be approximately 33 meters, which is very close to the effect observed for each of the three drug classes we evaluated, as well as the apparent benefit conferred by combination therapy relative to continuation of monotherapy in patients already on monotherapy. Another recent study suggested a threshold of 41.8 m for change in 6MWD to result in a reduction in clinical events.[216] These recent findings suggest that there may be some question as to the extent to which the statistically significant improvements in 6MWD associated with treatment in clinical trials is clinically meaningful. The paucity of evidence about minimal important differences applies especially to the intermediate outcomes assessed by right heart catheterization. The evidence base for KQ 3 was also limited by nonstandardized and nonsystematic reporting of adverse events.

Although we did not find evidence for publication bias in a funnel plot of 6MWD outcomes, this does not ensure the absence of selective reporting. Modest but statistically significant effects seen in extant studies might nevertheless result from biases in study design or selective reporting of results. The extent to which the funding source may be related to this is unclear from our data; a majority of treatment trials (68%) were industry funded.

Research Gaps

The available evidence leaves numerous gaps and areas for potential future research. We used the framework recommended by Robinson et al.[217] to identify gaps in evidence and describe why these gaps exist. Results are as follows:

KQ 1: Screening for PAH

- Patients at elevated risk for PAH, other than systemic sclerosis, have been seldom studied in screening test studies.
    - Consider cohort studies of testing for PH among high-risk populations other than those with systemic sclerosis, including patients with HIV, sickle cell anemia or trait portal hypertension, family history of PAH, or catecholaminergic drug use.
    - Different populations may have different risks of PAH and different benefits from screening; in studies where heterogeneous populations are included, the effectiveness of screening should be examined according to risk factor.
- Relatively few data exist on screening of asymptomatic patients with a combination of echocardiography and biomarker testing.
    - Consider cohort studies that apply echocardiography and biomarker screening in a coordinated or algorithmic way, and studies that verify diagnosis in at least a sample of test-negative patients by RHC or lengthy followup.
    - Future tests of the added value of biomarkers should use well-validated echocardiography parameters as a screening test, including estimates of pulmonary artery pressures (sPAP, TG, and TRV) and pulmonary vascular resistance (TRV/VTI_{RVOT}).
- Studies of echocardiography for diagnosis of PH have focused on the association of single measures or parameters at a time rather than an integrated diagnostic assessment based on an entire exam and multiple echocardiographic measures or parameters.
    - Consider studies that evaluate a global echocardiographic assessment based not only on sPAP but also on right heart chamber size wall thickness and function, estimated PVR, and left heart measures.
    - Consider further development of data on the use of echocardiography to measure exercise response to sPAP.
    - Consider further development of echocardiographic estimation of mPAP, which would better align with the diagnostic criteria for PAH.
    - Consider studies of additional promising measures such as end diastolic pulmonary regurgitation gradient, mean tricuspid regurgitation gradient, and Doppler tissue imaging of the tricuspid annulus.

KQ 2: Management of PAH

- Echocardiographic- and BNP-guided treatment strategies have not been explicitly tested.
    - Consider cohort studies evaluating prognosis as well as treatment trials examining association of baseline echocardiographic parameters and BNP levels to response to treatment.
- Other imaging modalities, such as magnetic resonance imaging, have been little studied as an alternative noninvasive test to assess RV function.

- Cardiopulmonary exercise testing and exercise echocardiography have relatively few data, uncertain clinical utility, and relationship to PH diagnostic criteria.
    - Consider validation studies to demonstrate prognostic value particularly for patients with normal resting echocardiography but abnormal exercise echocardiography.

KQ 3: Pharmacotherapy for PAH

- Relatively few data exist on the efficacy of treating PAH early in the disease course (WHO functional class I-II).
    - Improved data on efficacy of early PAH would strengthen linkage to efficacy of screening testing.
    - Consider treatment trials in early stage PAH, particularly among patients identified by case finding or screening interventions.
- Relatively few data exist on children with persistent PH or congenital heart disease.
    - Consider controlled trials in children.
- Few treatment trials address direct comparison of alternative drug treatment, particularly for PAH patients early in the disease course.
    - Consider trials designed to compare clinical alternative treatments to permit more evidence-based treatment selection such as head-to-head treatment comparisons rather than placebo-control or combination versus monotherapy trials.
- The majority of RCTs thus far have not collected adequate surrogate data and have failed to demonstrate therapeutic gain in terms of definitive endpoints.
    - Consider including biomarker and imaging techniques with conventional clinical outcomes to improve data on validity and responsiveness of surrogate outcomes.
- Few data are available about differences in response to treatment based on patient characteristics from trials.
    - Consider subgroup analysis of treatment efficacy by WHO functional class, underlying etiology, and other patient-level factors.
- Data on the efficacy of combination treatments are limited.
    - Consider more combination treatment trials, in particular trials with clear criteria for starting combination therapy and trials in patients who have not failed monotherapy.
- The duration of controlled trial efficacy data are limited.
    - Consider, particularly for clinically relevant comparisons (e.g., head-to-head treatment or combo versus monotherapy trials), longer term followup studies that retain randomized group comparisons while assessing long-term efficacy.

Conclusions

Further research is needed to confirm the single good-quality study suggesting that echocardiography and the biomarker NT-proBNP in combination may be sufficiently accurate to rule out PAH when testing symptomatic patients. In asymptomatic populations, more research is needed to draw conclusions regarding the effectiveness for screening. BNP, RA size, the presence of pericardial effusion and uric acid had prognostic value in patients with PAH, but other echocardiographic parameters and biomarkers either were not predictive or had insufficient data. Although no treatments demonstrate a strong and consistent mortality reduction, many are

associated with improved 6MWD and reduced hospitalization rates. Comparisons of different drug combinations are inconclusive regarding a mortality reduction but suggest an improvement in 6MWD compared with continuation of monotherapy.

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Abbreviations

6MWD	6-minute walk distance
AHRQ	Agency for Healthcare Research and Quality
BID	two times per day
BNP	B-type natriuretic peptide
CI	confidence interval
CHF	congestive heart failure
COPD	chronic obstructive pulmonary disease
CTEPH	chronic thromboembolic pulmonary hypertension
CVD	collagen vascular disease
DLCO	diffusion capacity of the lung for carbon monoxide
FAC	fractional area change
FC	functional class
HR	hazard ratio
HRQOL	health-related quality of life
IQR	interquartile range
KQ	Key Question
MI	myocardial infarction
MIF	migration inhibitory factor
mo	month/months
mPAP	mean pulmonary artery pressure
MPI	myocardial performance index
NA	not applicable
NR	not reported
NT-proBNP	N-terminal pro-B-type natriuretic peptide
NYHA	New York Heart Association
OR	odds ratio
PAH	pulmonary arterial hypertension
PADP	pulmonary artery diastolic pressure
PASP	pulmonary artery systolic pressure
PCWP	pulmonary capillary wedge pressure
PH	pulmonary hypertension
PPH	primary pulmonary hypertension
PVR	pulmonary vascular resistance
QOL	quality of life
RA	right atrium
RAP	right atrial pressure
RHC	right heart catheterization
RIMP	right index of myocardial performance
RR	risk ratio
RV	right ventricle
RVEF	right ventricle ejection fraction
S’	tricuspid lateral annular systolic velocity
SD	standard deviation
SEM	standard error of the mean

SOE	strength of evidence
sPAP	systolic pulmonary artery pressure
SSc	systemic sclerosis
TAPSE	tricuspid annular plane systolic excursion
TDI	tissue Doppler imaging
TID	three times per day
TEP	Technical Expert Panel
TG	tricuspid gradient
TRV	tricuspid regurgitant jet velocity
VSD	ventricular septal defect
VTI_{RVOT}	velocity-time integral of right ventricular outflow tract
yr	year/years

Appendix A. Exact Search Strings

PubMed® search strategy (August 14, 2012)

Table A-1. PubMed search terms for KQ 1: Screening for PAH

Set #	Terms
#1	("Hypertension, Pulmonary"[Mesh] OR "Idiopathic pulmonary hypertension "[Supplementary Concept]) OR ("pulmonary hypertension"[ti] OR "pulmonary arterial hypertension"[ti] OR "pulmonary artery hypertension"[ti]) OR (("hypertension, pulmonary"[MeSH Terms] OR "pulmonary hypertension"[tiab] OR ("pulmonary"[tiab] AND "hypertension"[tiab])) AND (pah[ti] OR ipah[ti] OR pph[ti]))
#2	"Echocardiography"[Mesh] OR echocardiogram[tiab] OR echocardiography[tiab] OR TTE[tiab] OR TEE[tiab] OR echo[tiab]
#3	(sensitive[tiab] OR sensitivity[tiab] OR specificity[tiab] OR "sensitivity and specificity"[MeSH Terms] OR diagnosis[tiab] OR diagnostic[tiab] OR diagnosed[tiab] OR "diagnosis"[MeSH Terms] OR "diagnosis"[Subheading] OR screening[tiab] OR screen[tiab] OR "mass screening"[MeSH Terms] OR "cross-sectional studies"[MeSH Terms] OR cross-sectional[tiab]) NOT (Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp] OR Comment[ptyp]) NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms])
#4	#1 AND #2 AND #3 English, Publication Date from 1995 to 2011
#5	"Natriuretic Peptides"[Mesh] OR "Uric Acid"[Mesh] OR "Troponin"[Mesh] OR "Nitric Oxide"[Mesh] OR "dimethylarginine"[Supplementary Concept] OR "fibrin fragment D"[Supplementary Concept] OR "Serotonin"[Mesh] OR "von Willebrand Factor"[Mesh] OR "Thrombomodulin"[Mesh] OR "Selectins"[Mesh] OR "C-Reactive Protein"[Mesh] OR "Isoprostanes"[Mesh] OR "Interleukins"[Mesh] OR "Endothelin-1"[Mesh] OR "Cyclic GMP"[Mesh] OR (Natriuretic[tiab] AND Peptides[tiab]) OR (Natriuretic[tiab] AND Peptide[tiab]) OR "Uric Acid"[tiab] OR "Troponin"[tiab] OR "Nitric Oxide"[tiab] OR "dimethylarginine"[tiab] OR "d-dimer"[tiab] OR "Serotonin"[tiab] OR "Willebrand Factor"[tiab] OR "Thrombomodulin"[tiab] OR "Selectins"[tiab] OR "Selectin"[tiab] AND R[All Fields] AND "C-Reactive Protein"[tiab] OR "Isoprostanes"[tiab] OR Isoprostane[tiab] OR "Interleukins"[tiab] OR "Interleukin"[tiab] OR "Endothelin-1"[tiab] OR "Cyclic GMP"[tiab] OR cgmp[tiab] OR (soluble[tiab] AND ligand[tiab]) OR (endothelial[tiab] AND dysfunction[tiab]) OR "Biological Markers"[Mesh] OR (biological[tiab] AND (marker[tiab] OR markers[tiab])) OR biomarker[tiab] OR biomarkers[tiab]
#6	#1 AND #5 AND #3 English, Publication Date from 1995 to 2011
#7	#1 AND #2 AND #5 English, Publication Date from 1995 to 2011

Table A-2. PubMed search terms for KQ 2: Management of PAH

Set #	Terms
#1	("Hypertension, Pulmonary"[Mesh] OR "Idiopathic pulmonary hypertension "[Supplementary Concept]) OR ("pulmonary hypertension"[ti] OR "pulmonary arterial hypertension"[ti] OR "pulmonary artery hypertension"[ti]) OR (("hypertension, pulmonary"[MeSH Terms] OR "pulmonary hypertension"[tiab] OR ("pulmonary"[tiab] AND "hypertension"[tiab])) AND (pah[ti] OR ipah[ti] OR pph[ti]))
#2	"Echocardiography"[Mesh] OR echocardiogram[tiab] OR echocardiography[tiab] OR TTE[tiab] OR TEE[tiab] OR echo[tiab]
#3	#1 AND #2 English, Publication Date from 1995 to 2011
#4	(clinical[tiab] AND decision[tiab]) OR (clinical[tiab] AND decisions[tiab]) OR (decision[tiab] AND making[tiab]) OR screening[tiab] OR screen[tiab] OR "mass screening"[MeSH Terms] OR management[tiab] OR "treatment outcome"[MeSH Terms] OR outcome[tiab] OR outcomes[tiab] OR "Patient Care Management"[Mesh] OR treatment[tiab] OR therapy[tiab]
#5	#3 AND #4 English, Publication Date from 1995 to 2011

Set #	Terms
#6	"Natriuretic Peptides"[Mesh] OR "Uric Acid"[Mesh] OR "Troponin"[Mesh] OR "Nitric Oxide"[Mesh] OR "dimethylarginine"[Supplementary Concept] OR "fibrin fragment D"[Supplementary Concept] OR "Serotonin"[Mesh] OR "von Willebrand Factor"[Mesh] OR "Thrombomodulin"[Mesh] OR "Selectins"[Mesh] OR "C-Reactive Protein"[Mesh] OR "Isoprostanes"[Mesh] OR "Interleukins"[Mesh] OR "Endothelin-1"[Mesh] OR "Cyclic GMP"[Mesh] OR (Natriuretic[tiab] AND Peptides[tiab]) OR (Natriuretic[tiab] AND Peptide[tiab]) OR "Uric Acid"[tiab] OR "Troponin"[tiab] OR "Nitric Oxide"[tiab] OR "dimethylarginine"[tiab] OR "d-dimer"[tiab] OR "Serotonin"[tiab] OR "Willebrand Factor"[tiab] OR "Thrombomodulin"[tiab] OR "Selectins"[tiab] OR "Selectin"[tiab] AND R[All Fields] AND "C-Reactive Protein"[tiab] OR "Isoprostanes"[tiab] OR Isoprostane[tiab] OR "Interleukins"[tiab] OR "Interleukin"[tiab] OR "Endothelin-1"[tiab] OR "Cyclic GMP"[tiab] OR cgmp[tiab] OR (soluble[tiab] AND ligand[tiab]) OR (endothelial[tiab] AND dysfunction[tiab]) OR "Biological Markers"[Mesh] OR (biological[tiab] AND (marker[tiab] OR markers[tiab])) OR biomarker[tiab] OR biomarkers[tiab]
#7	#1 AND #6 English, Publication Date from 1995 to 2011
#8	#7 AND #4 English, Publication Date from 1995 to 2011
#9	#1 AND #2 AND #6 English, Publication Date from 1995 to 2011
#10	#1 AND (#2 OR #6) English, Publication Date from 1995 to 2011
#11	(sensitive[tiab] OR sensitivity[tiab] OR specificity[tiab] OR "sensitivity and specificity"[MeSH Terms] OR diagnosis[tiab] OR diagnostic[tiab] OR diagnosed[tiab] OR "diagnosis"[MeSH Terms] OR "diagnosis"[Subheading] OR screening[tiab] OR screen[tiab] OR "mass screening"[MeSH Terms] OR "cross-sectional studies"[MeSH Terms] OR cross-sectional[tiab]) NOT (Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp] OR Comment[ptyp]) NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms])
#12	#1 AND (#2 OR #6) AND (#3 OR #11) English, Publication Date from 1995 to 2011

Table A-3. PubMed search terms for KQ 3: Monotherapy vs. Combination Therapy for PAH

Set #	Terms
#1	("Hypertension, Pulmonary"[Mesh] OR "Idiopathic pulmonary hypertension "[Supplementary Concept]) OR ("pulmonary hypertension"[ti] OR "pulmonary arterial hypertension"[ti] OR "pulmonary artery hypertension"[ti]) OR (("hypertension, pulmonary"[MeSH Terms] OR "pulmonary hypertension"[tiab] OR ("pulmonary"[tiab] AND "hypertension"[tiab])) AND (pah[ti] OR ipah[ti] OR pph[ti]))
#2	("Calcium Channel Blockers"[Mesh] OR "Calcium Channel Blockers"[Pharmacological Action] OR calcium channel blockers[tiab] OR calcium channel blocker[tiab] OR nifedipine[tiab] OR diltiazem[tiab] OR amlodipine[tiab]) OR ("prostaglandins"[MeSH Terms] OR "prostaglandins"[tiab] OR "prostaglandins"[tiab] OR "prostanoid"[tiab] OR "prostanoids"[tiab] OR "epoprostenol"[MeSH Terms] OR "epoprostenol"[tiab] OR "prostacyclin"[tiab] OR "treprostinil"[Supplementary Concept] OR "treprostinil"[tiab] OR "iloprost"[MeSH Terms] OR "iloprost"[tiab] OR "Receptors, Endothelin/antagonists and inhibitors"[Mesh] OR (("endothelins"[MeSH Terms] OR "endothelins"[tiab] OR "endothelin"[tiab]) AND (antagonist[tiab] OR "antagonists"[tiab] OR "inhibitors"[tiab])) OR "bosentan"[Supplementary Concept] OR "bosentan"[tiab] OR "ambrisentan"[Supplementary Concept] OR "ambrisentan"[tiab] OR "phosphodiesterase inhibitors"[MeSH Terms] OR ("phosphodiesterase"[tiab] AND "inhibitors"[tiab]) OR "phosphodiesterase inhibitors"[tiab] OR "phosphodiesterase inhibitors"[Pharmacological Action] OR "phosphodiesterase 5 inhibitors"[tiab] OR "phosphoric diester hydrolases"[MeSH Terms] OR ("phosphoric"[tiab] AND "diester"[tiab] AND "hydrolases"[tiab]) OR (("phosphodiesterase"[tiab] OR "phosphodiesterases"[tiab]) AND (inhibitor[tiab] OR "antagonists and inhibitors"[Subheading] OR "antagonists"[tiab] OR "inhibitors"[tiab] OR antagonist[tiab])) OR (pde5[tiab] AND (inhibitor[tiab] OR "antagonists and inhibitors"[Subheading] OR "antagonists"[tiab] OR "antagonist"[tiab] OR "inhibitors"[tiab] OR "inhibitors"[tiab])) OR pde5i[tiab] OR "sildenafil"[Supplementary Concept] OR "sildenafil"[tiab] OR "tadalafil"[Supplementary Concept] OR "tadalafil"[tiab] OR "Vasodilator Agents"[Mesh:noexp] OR "Vasodilator Agents "[Pharmacological Action])

Set #	Terms
#3	(randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR randomization[tiab] OR randomisation[tiab] OR placebo[tiab] OR "drug therapy"[Subheading] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR Clinical trial[pt] OR "clinical trial"[tw] OR "clinical trials"[tw] OR "evaluation studies"[Publication Type] OR "evaluation studies as topic"[MeSH Terms] OR "evaluation study"[tw] OR evaluation studies[tw] OR "intervention studies"[MeSH Terms] OR "intervention study"[tw] OR "intervention studies"[tw] OR "case-control studies"[MeSH Terms] OR "case-control"[tw] OR "cohort studies"[MeSH Terms] OR cohort[tw] OR "longitudinal studies"[MeSH Terms] OR "longitudinal"[tw] OR longitudinally[tw] OR "prospective"[tw] OR prospectively[tw] OR "retrospective studies"[MeSH Terms] OR "retrospective"[tw] OR "follow up"[tw] OR "comparative study"[Publication Type] OR "comparative study"[tw] OR systematic[subset] OR "meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "meta-analysis"[tw] OR "meta-analyses"[tw]) NOT (Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp] OR Comment[ptyp]) NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms])
#4	#1 AND #2 AND #3 English, Publication Date from 1995 to 2011

Embase® search strategy (August 14, 2012)

Platform: Embase.com

Table A-4. Embase search terms for KQ 1: Screening for PAH

Set #	Terms
#1	'pulmonary hypertension'/exp OR "idiopathic pulmonary hypertension":ab,ti OR "pulmonary arterial hypertension":ab,ti OR "pulmonary artery hypertension":ab,ti OR "pulmonary hypertension":ab,ti OR pah:ab,ti OR ipah:ab,ti OR pph:ab,ti
#2	'echocardiography'/exp OR echocardiography:ab,ti OR echocardiogram:ab,ti OR echo:ab,ti OR TEE:ab,ti OR TEE:ab,ti
#3	('sensitivity and specificity'/exp OR diagnosis:de OR diagnostic:de OR 'screening'/exp OR 'cross-sectional study'/exp OR sensitive:ab,ti OR sensitive:ab,ti OR sensitivity:ab,ti OR specificity:ab,ti OR diagnosis:ab,ti OR diagnostic:ab,ti OR diagnosed:ab,ti OR screening:ab,ti OR screen:ab,ti OR cross-sectional:ab,ti OR likelihood:ab,ti) NOT 'editorial'/exp OR 'letter'/exp OR 'case report'/exp
#4	#1 AND #2 AND #3
#5	#1 AND #2 AND #3 AND [embase]/lim NOT [medline]/lim AND [humans]/lim AND [1995-2012]/py
#6	'natriuretic factor'/exp OR 'uric acid'/exp OR 'troponin'/exp OR 'nitric oxide'/exp OR '6 n,n` dimethylarginine'/exp OR 'serotonin'/exp OR 'von Willebrand factor'/exp OR 'C reactive protein'/exp OR 'isoprostane derivative'/exp OR 'interleukin derivative'/exp OR 'endothelin 1'/exp OR 'cyclic GMP'/exp OR 'thrombomodulin'/exp OR 'selectin'/exp OR 'biological marker'/exp OR “Natriuretic Peptides”:ab,ti OR “Natriuretic Peptide”:ab,ti OR “Uric Acid”:ab,ti OR Troponin:ab,ti OR “Nitric Oxide”:ab,ti OR dimethylarginine:ab,ti OR d-dimer:ab,ti OR Serotonin:ab,ti OR ”Willebrand Factor”:ab,ti OR Thrombomodulin:ab,ti OR Selectins:ab,ti OR Selectin:ab,ti OR “C-Reactive Protein”:ab,ti OR Isoprostanes:ab,ti OR Isoprostane:ab,ti OR Interleukins:ab,ti OR Interleukin:ab,ti OR Endothelin-1:ab,ti OR “Cyclic GMP”:ab,ti OR cgmp:ab,ti OR “soluble ligand”:ab,ti OR “biological marker”:ab,ti OR “biological markers”:ab,ti OR biomarker:ab,ti OR biomarkers:ab,ti OR “endothelial dysfunction”:ab,ti OR fibrin fragment:de
#7	#1 AND #6 AND #3
#8	#7 AND [embase]/lim NOT [medline]/lim AND [humans]/lim AND [1995-2012]/py
#9	#1 AND #2 AND #3 AND #6 AND [embase]/lim NOT [medline]/lim AND [humans]/lim AND [1995-2012]/py

Table A-5. Embase search terms for KQ 2: Management of PAH

Set #	Terms
#1	'pulmonary hypertension'/exp OR "idiopathic pulmonary hypertension":ab,ti OR "pulmonary arterial hypertension":ab,ti OR "pulmonary artery hypertension":ab,ti OR "pulmonary hypertension":ab,ti OR pah:ab,ti OR ipah:ab,ti OR pph:ab,ti
#2	'echocardiography'/exp OR echocardiography:ab,ti OR echocardiogram:ab,ti OR echo:ab,ti OR TEE:ab,ti OR TEE:ab,ti

Set #	Terms
#3	'treatment outcome'/exp OR 'clinical decision making'/exp OR 'decision making'/exp OR 'patient care'/de OR (clinical:ab,ti AND decision:ab,ti) OR (clinical:ab,ti AND decisions:ab,ti) OR (decision:ab,ti AND making:ab,ti) OR management:ab,ti OR "treatment outcome":ab,ti OR outcome:ab,ti OR outcomes:ab,ti OR treatment:ab,ti OR therapy:ab,ti OR 'controlled clinical trial'/exp OR 'clinical trial'/exp OR 'evidence based medicine'/exp
#4	#3 NOT ('editorial'/exp OR 'letter'/exp OR 'case report'/exp)
#5	#1 AND #2 AND #4
#6	#5 AND [embase]/lim NOT [medline]/lim AND [humans]/lim AND [1995-2012]/py
#7	'natriuretic factor'/exp OR 'uric acid'/exp OR 'troponin'/exp OR 'nitric oxide'/exp OR '6 n,n` dimethylarginine'/exp OR 'serotonin'/exp OR 'von Willebrand factor'/exp OR 'C reactive protein'/exp OR 'isoprostane derivative'/exp OR 'interleukin derivative'/exp OR 'endothelin 1'/exp OR 'cyclic GMP'/exp OR 'thrombomodulin'/exp OR 'selectin'/exp OR 'biological marker'/exp OR "Natriuretic Peptides":ab,ti OR "Natriuretic Peptide":ab,ti OR "Uric Acid":ab,ti OR Troponin:ab,ti OR "Nitric Oxide":ab,ti OR dimethylarginine:ab,ti OR d-dimer:ab,ti OR Serotonin:ab,ti OR "Willebrand Factor":ab,ti OR Thrombomodulin:ab,ti OR Selectins:ab,ti OR Selectin:ab,ti OR "C-Reactive Protein":ab,ti OR Isoprostanes:ab,ti OR Isoprostane:ab,ti OR Interleukins:ab,ti OR Interleukin:ab,ti OR Endothelin-1:ab,ti OR "Cyclic GMP":ab,ti OR cgmp:ab,ti OR "soluble ligand":ab,ti OR "biological marker":ab,ti OR "biological markers":ab,ti OR biomarker:ab,ti OR biomarkers:ab,ti OR "endothelial dysfunction":ab,ti OR fibrin fragment:de
#8	#1 AND #7 AND #4
#9	#8 AND [embase]/lim NOT [medline]/lim AND [humans]/lim AND [1995-2012]/py
#10	#1 AND #2 AND #7 AND [english]/lim AND [1995-2012]/py AND [embase]/lim NOT [medline]/lim AND [humans]/lim

Table A-6. Embase search terms for KQ 3: Monotherapy vs. Combination Therapy for PAH

Set #	Terms
#1	'pulmonary hypertension'/exp OR "idiopathic pulmonary hypertension":ab,ti OR "pulmonary arterial hypertension":ab,ti OR "pulmonary artery hypertension":ab,ti OR "pulmonary hypertension":ab,ti OR pah:ab,ti OR ipah:ab,ti
#2	'prostaglandin'/exp OR 'iloprost'/exp OR 'endothelin receptor'/exp OR 'bosentan'/exp OR 'ambrisentan'/exp OR 'phosphodiesterase inhibitor'/exp OR 'phosphodiesterase'/exp OR 'sildenafil'/exp OR 'tadalafil'/exp OR 'vasodilator agent'/exp or "prostaglandin":ab,ti OR "prostaglandins":ab,ti OR "prostanoid":ab,ti OR "prostanoids":ab,ti OR "epoprostenol":ab,ti OR "prostacyclin":ab,ti OR "treprostinil":ab,ti OR "iloprost":ab,ti OR "bosentan":ab,ti OR "ambrisentan":ab,ti OR ("phosphodiesterase":ab,ti AND "inhibitors":ab,ti) OR "phosphodiesterase inhibitors":ab,ti OR "phosphodiesterase 5 inhibitors":ab,ti OR ("phosphoric":ab,ti AND "diester":ab,ti AND "hydrolases":ab,ti) OR "sildenafil":ab,ti OR "tadalafil":ab,ti OR (("phosphodiesterase":ab,ti OR "phosphodiesterases":ab,ti OR "endothelins":ab,ti OR "endothelin":ab,ti OR pde5:ab,ti) AND (inhibitor:ab,ti OR "antagonists":ab,ti OR "inhibitors":ab,ti OR antagonist:ab,ti))
#3	'calcium channel blocking agent'/exp OR 'calcium channel blocker':ab,ti OR 'calcium channel blockers':ab,ti OR Amlodipine:ab,ti OR Amrinone:ab,ti OR anandamide:ab,ti OR anipamil:ab,ti OR azimilide:ab,ti OR Bencyclane:ab,ti OR benidipine:ab,ti OR Bepridil:ab,ti OR berbamine:ab,ti OR canadine:ab,ti OR 'carboxyamido-triazole':ab,ti OR caroverine:ab,ti OR cilnidipine:ab,ti OR Cinnarizine:ab,ti OR clentiazem:ab,ti OR Conotoxins:ab,ti OR darodipine:ab,ti OR dauricine:ab,ti OR devapamil:ab,ti OR Diltiazem:ab,ti OR dimeditiapramine:ab,ti OR dotarizine:ab,ti OR efonidipine:ab,ti OR emopamil:ab,ti OR enpiperate:ab,ti OR eperisone:ab,ti OR falipamil:ab,ti OR fantofarone:ab,ti OR fasudil:ab,ti OR Felodipine:ab,ti OR 'fenamic acid':ab,ti OR Fendiline:ab,ti OR Flunarizine:ab,ti OR fosfedil:ab,ti OR gabapentin:ab,ti OR Gallopamil:ab,ti OR Isradipine:ab,ti OR lacidipine:ab,ti OR lamotrigine:ab,ti OR lercanidipine:ab,ti OR Lidoflazine:ab,ti OR 'Magnesium Sulfate':ab,ti OR manidipine:ab,ti OR manoalide:ab,ti OR mepirodipine:ab,ti OR Mibefradil:ab,ti OR monatepil:ab,ti OR naftopidil:ab,ti OR Nicardipine:ab,ti OR Nifedipine:ab,ti OR niguldipine:ab,ti OR niludipin:ab,ti OR nilvadipine:ab,ti OR Nimodipine:ab,ti OR Nisoldipine:ab,ti OR Nitrendipine:ab,ti OR norverapamil:ab,ti OR ochratoxin:ab,ti OR octylonium:ab,ti OR 'omega-Agatoxin':ab,ti OR 'omega-Conotoxin':ab,ti OR 'omega-Conotoxins':ab,ti OR osthol:ab,ti OR oxodipine:ab,ti OR Perhexiline:ab,ti OR pinaverium:ab,ti OR piperidine:ab,ti OR pranidipine:ab,ti OR Prenylamine:ab,ti OR ' risedronic acid':ab,ti OR ryodipine:ab,ti OR sesamodil:ab,ti OR stepholidine:ab,ti OR terodiline:ab,ti OR tetrahydropalmatine:ab,ti OR tetrandrine:ab,ti OR 'tolfenamic acid':ab,ti OR tranilast:ab,ti OR Verapamil:ab,ti OR ziconotide:ab,ti

Set #	Terms
#4	('randomized controlled trial'/exp OR 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'single blind procedure'/exp OR random*:ab,ti OR factorial*:ab,ti OR crossover*:ab,ti OR (cross NEAR/1 over*):ab,ti OR placebo*:ab,ti OR (doubl* NEAR/1 blind*):ab,ti OR (singl* NEAR/1 blind*):ab,ti OR assign*:ab,ti OR allocat*:ab,ti OR volunteer*:ab,ti OR 'clinical study'/exp OR "clinical trial":ti,ab OR "clinical trials":ti,ab OR 'controlled study'/exp OR 'evaluation'/exp OR "evaluation study":ab,ti OR "evaluation studies":ab,ti OR "intervention study":ab,ti OR "intervention studies":ab,ti OR "case control":ab,ti OR 'cohort analysis'/exp OR cohort:ab,ti OR longitudinal*:ab,ti OR prospective:ab,ti OR prospectively:ab,ti OR retrospective:ab,ti OR 'follow up'/exp OR "follow up":ab,ti OR 'comparative effectiveness'/exp OR 'comparative study'/exp OR "comparative study":ab,ti OR "comparative studies":ab,ti OR 'evidence based medicine'/exp OR "systematic review":ab,ti OR "meta-analysis":ab,ti OR "meta-analyses":ab,ti) NOT ('case report'/exp OR 'case study'/exp OR 'editorial'/exp OR 'letter'/exp OR 'note'/exp)
#5	#1 AND (#2 OR #3) AND #4
#6	#5 AND [embase]/lim NOT [medline]/lim AND [humans]/lim AND [1995-2012]/py

Cochrane Database of Systematic Reviews (August 14, 2012)

Platform: Wiley

Table A-7. Cochrane search terms for KQs 1 and 2: Screening and Management of PAH

Set #	Terms
#1	MeSH descriptor Hypertension, Pulmonary explode all trees OR (pulmonary hypertension):ti,ab,kw OR (idiopathic pulmonary hypertension):ti,ab,kw OR (pulmonary arterial hypertension):ti,ab,kw OR (pulmonary artery hypertension):ti,ab,kw OR pah:ti,ab,kw OR ipah:ti,ab,kw
#2	MeSH descriptor echocardiography explode all trees OR echocardiography:ti,ab,kw OR echocardiogram:ti,ab,kw OR echo:ti,ab,kw OR TEE:ti,ab,kw OR TEE:ti,ab,kw
#3	#1 AND #2 AND (Cochrane Reviews, other reviews) AND 1995-2012
#4	MeSH descriptor Natriuretic Peptides explode all trees OR MeSH descriptor Uric Acid explode all trees OR MeSH descriptor Troponin explode all trees OR MeSH descriptor Nitric Oxide explode all trees OR MeSH descriptor Serotonin explode all trees OR MeSH descriptor von Willebrand Factor explode all trees OR MeSH descriptor C-Reactive Protein explode all trees OR MeSH descriptor Isoprostanes explode all trees OR MeSH descriptor Interleukins explode all trees OR MeSH descriptor Endothelins explode all trees OR MeSH descriptor Cyclic GMP explode all trees OR MeSH descriptor Thrombomodulin explode all trees OR MeSH descriptor Selectins explode all trees OR MeSH descriptor Biological Markers explode all trees OR (Natriuretic Peptides):ti,ab,kw OR (Natriuretic Peptide):ti,ab,kw OR (Uric Acid):ti,ab,kw OR Troponin:ti,ab,kw OR (Nitric Oxide):ti,ab,kw OR dimethylarginine:ti,ab,kw OR (d-dimer):ti,ab,kw OR Serotonin:ti,ab,kw OR (Willebrand Factor):ti,ab,kw OR Thrombomodulin:ti,ab,kw OR Selectins:ti,ab,kw OR Selectin:ti,ab,kw OR (C-Reactive Protein):ti,ab,kw OR Isoprostanes:ti,ab,kw OR Isoprostane:ti,ab,kw OR Interleukins:ti,ab,kw OR Interleukin:ti,ab,kw OR (Endothelin-1):ti,ab,kw OR (Cyclic GMP):ti,ab,kw OR cgmp:ti,ab,kw OR (soluble ligand):ti,ab,kw OR (biological marker):ti,ab,kw OR (biological markers):ti,ab,kw OR biomarker:ti,ab,kw OR biomarkers:ti,ab,kw OR (endothelial dysfunction):ti,ab,kw OR (fibrin fragment):ti,ab,kw
#5	#1 AND #4 AND (Cochrane Reviews, other reviews) AND 1995-2012
#6	#1 AND #2 AND #4 AND (Cochrane Reviews, other reviews) AND 1995-2012

Table A-8. Cochrane search terms for KQ 3: Monotherapy vs. Combination Therapy for PAH

Set #	Terms
#1	MeSH descriptor Hypertension, Pulmonary explode all trees OR (pulmonary hypertension):ti,ab,kw OR (idiopathic pulmonary hypertension):ti,ab,kw OR (pulmonary arterial hypertension):ti,ab,kw OR (pulmonary artery hypertension):ti,ab,kw OR pah:ti,ab,kw OR ipah:ti,ab,kw
#2	bosentan:ti,ab,kw OR ambrisentan:ti,ab,kw OR phosphodiesterase:ti,ab,kw OR sildenafil:ti,ab,kw OR tadalafil:ti,ab,kw OR (vasodilator agent):ti,ab,kw or prostaglandin:ti,ab,kw OR prostaglandins:ti,ab,kw OR prostanoid:ti,ab,kw OR prostanoids:ti,ab,kw OR epoprostenol:ti,ab,kw OR prostacyclin:ti,ab,kw OR treprostinil:ti,ab,kw OR iloprost:ti,ab,kw OR bosentan:ti,ab,kw OR ambrisentan:ti,ab,kw OR sildenafil:ti,ab,kw OR tadalafil:ti,ab,kw OR endothelins:ti,ab,kw OR endothelin:ti,ab,kw OR pde5:ti,ab,kw OR MeSH descriptor Vasodilator Agents explode all trees OR MeSH descriptor Endothelins explode all trees OR MeSH descriptor Prostaglandins explode all trees OR MeSH descriptor Hydrolases explode all trees OR MeSH descriptor Phosphodiesterase Inhibitors explode all trees
#3	Amlodipine:ti,ab,kw OR Amrinone:ti,ab,kw OR anandamide:ti,ab,kw OR anipamil:ti,ab,kw OR azimilide:ti,ab,kw OR Bencyclane:ti,ab,kw OR benidipine:ti,ab,kw OR Bepridil:ti,ab,kw OR berbamine:ti,ab,kw OR canadine:ti,ab,kw OR (carboxyamido-triazole):ti,ab,kw OR caroverine:ti,ab,kw OR cilnidipine:ti,ab,kw OR Cinnarizine:ti,ab,kw OR clentiazem:ti,ab,kw OR Conotoxins:ti,ab,kw OR darodipine:ti,ab,kw OR dauricine:ti,ab,kw OR devapamil:ti,ab,kw OR Diltiazem:ti,ab,kw OR dimeditiapramine:ti,ab,kw OR dotarizine:ti,ab,kw OR efonidipine:ti,ab,kw OR emopamil:ti,ab,kw OR enpiperate:ti,ab,kw OR eperisone:ti,ab,kw OR falipamil:ti,ab,kw OR fantofarone:ti,ab,kw OR fasudil:ti,ab,kw OR Felodipine:ti,ab,kw OR (fenamic acid):ti,ab,kw OR Fendiline:ti,ab,kw OR Flunarizine:ti,ab,kw OR fosfedil:ti,ab,kw OR gabapentin:ti,ab,kw OR Gallopamil:ti,ab,kw OR Isradipine:ti,ab,kw OR lacidipine:ti,ab,kw OR lamotrigine:ti,ab,kw OR lercanidipine:ti,ab,kw OR Lidoflazine:ti,ab,kw OR (Magnesium Sulfate):ti,ab,kw OR manidipine:ti,ab,kw OR manoalide:ti,ab,kw OR mepirodipine:ti,ab,kw OR Mibefradil:ti,ab,kw OR monatepil:ti,ab,kw OR naftopidil:ti,ab,kw OR Nicardipine:ti,ab,kw OR Nifedipine:ti,ab,kw OR niguldipine:ti,ab,kw OR niludipin:ti,ab,kw OR nilvadipine:ti,ab,kw OR Nimodipine:ti,ab,kw OR Nisoldipine:ti,ab,kw OR Nitrendipine:ti,ab,kw OR norverapamil:ti,ab,kw OR ochratoxin:ti,ab,kw OR octylonium:ti,ab,kw OR (omega-Agatoxin):ti,ab,kw OR (omega-Conotoxin):ti,ab,kw OR (omega-Conotoxins):ti,ab,kw OR osthol:ti,ab,kw OR oxodipine:ti,ab,kw OR Perhexiline:ti,ab,kw OR pinaverium:ti,ab,kw OR piperidine:ti,ab,kw OR pranidipine:ti,ab,kw OR Prenylamine:ti,ab,kw OR (risedronic acid):ti,ab,kw OR ryodipine:ti,ab,kw OR sesamodil:ti,ab,kw OR stepholidine:ti,ab,kw OR terodiline:ti,ab,kw OR tetrahydropalmatine:ti,ab,kw OR tetrandrine:ti,ab,kw OR (tolfenamic acid):ti,ab,kw OR tranilast:ti,ab,kw OR Verapamil:ti,ab,kw OR ziconotide:ti,ab,kw OR MeSH descriptor Calcium Channel Blockers explode all trees
#4	#1 AND (#2 OR #3) AND (Cochrane Reviews, other reviews) AND 1995-2012

Appendix B. Data Abstraction Elements

I. Study Characteristics

- First Author (Last Name) and Year of Publication
- Additional Articles Used in This Abstraction
- Study Sites
  - Single Center; Multicenter; Not reported/Unclear
- Number of Sites
- Geographical Location (Select all applicable geographic regions)
  - US; Canada; UK; Europe; South America; Central America; Asia; Africa; Australia/New Zealand; Not reported/Unclear; Other (Specify)
- Funding Source (Check all that apply)
  - Government; Private Foundation; Industry; Not reported; Other (Specify)
- Enrollment Approach (Check all that apply)
  - Consecutive patients; Convenience sample (not explicitly consecutive); Other (Specify); Not reported/Unclear
- Study Inclusion and Exclusion Criteria
  - Copy/paste inclusion/exclusion criteria as reported in the article
- Study Design
  - RCT; Cohort; Other (describe)
- Study Enrollment/Study Completion
  - Total, Treatment Arm 1, 2, 3, 4
    Assessed for eligibility (N)
    Eligible (N)
    Enrolled/Randomized (N)
    Completed follow-up (N)
- Subgroup Analysis (Yes/No)
  - If Yes: Describe the subgroups reported
- Key Question Applicability
  - KQ1; KQ2; KQ3
    KQ 1. For patients with suspected pulmonary arterial hypertension (PAH) and asymptomatic patients at high risk for PAH, what is the comparative effectiveness and safety of echocardiography versus echocardiography plus biomarkers as screening modalities before right heart catheterization to establish the diagnosis of PAH (diagnostic accuracy efficacy)?
    KQ 2. For patients with PAH, what is the comparative effectiveness and safety of (a) echocardiography plus clinical assessment (e.g., functional class, dyspnea, 6-minute walk test) versus biomarkers plus clinical assessment and (b) echocardiography plus clinical assessment versus echocardiography plus biomarkers and clinical assessment in managing PAH (diagnostic thinking efficacy and therapeutic efficacy) and on intermediate-term (≤90 days) and long-term (>90 days) patient outcomes (patient outcome efficacy)?
    KQ 3. For patients with PAH, what is the comparative effectiveness and safety of monotherapy or combination therapy for PAH using calcium-channel blockers, prostanoids, endothelin receptor antagonists, or phosphodiesterase inhibitors on intermediate-term and long-term patient outcomes?
- Comments

II. Baseline Characteristics

- Total, Study Arm 1, Study Arm 2, Study Arm 3, Study Arm 4
    - Patient Population
        Describe the population for each study arm
    - Number of Subjects
        N
            - Total
            - Female
            - Male
            - Adults
            - Children
            - Mixed

        %
            - Female
            - Male
            - Adults
            - Children
            - Mixed
    - Age
        Mean
            - SD
            - SE

        Median
            - IQR
    - Ethnicity
        Hispanic or Latino
            - N
            - %

        No Hispanic or Latino
            - N
            - %
    - Race
        Black/African American
            - N
            - %

        American Indian or Alaska Native
            - N
            - %

        Asian
            - N
            - %

        Native Hawaiian or other Pacific Islander
            - N
            - %

        White
            - N
            - %

        Multiracial
            - N

- %

Other (Specify)

- N
- %

- Baseline Characteristics

BMI

- Mean
  - SD
  - SE
- Median
  - IQR

WHO Functional Class (N)

- Class I
- Class II
- Class III
- Class IV

NYHA Functional Classification (N)

- Class I
- Class II

Class III

- Class IV

PAH Etiology (N)

- Idiopathic (1.1)
- Familial (1.2)
- Collagen vascular disease (1.3.1)
- Congenital shunts (1.3.2)
- Portal HTN (1.3.3)
- HIV (1.3.4)
- Drugs/toxins (1.3.5)
- Venous or capillary disease (1.4.x)
- Pulmonary HTN of newborn (1.5)
- Thromboembolic (4.x)
- Other

Disease Duration

- Mean
  - SD
  - SE
- Median
  - IQR

Obesity (e.g. N with BMI>30)

- Mean
  - SD
  - SE
- Median
  - IQR
- N

Prior Treatments (N)

- Calcium channel blockers
- Diuretics

- Digoxin
- Prostanoids
- Endothelin antagonists
- Phosphodiesterase inhibitors
- Anticoagulants
- Other

Left ventricular ejection fraction (LVEF)

- Mean
  - SD
  - SE
- Median
  - IQR

Other (Specify)

- Mean
  - SD
  - SE
- Median
  - IQR
- N

- Comments

III. Intervention Characteristics

- Study Arm 1, Study Arm 2, Study Arm 3, Study Arm 4
  - Medical Therapy Intervention

    Amlodipine; Diltiazem; Nifedipine; Verapamil; Epoprostenol; Treprostinil; Iloprost; Bosentan; Ambrisentan; Sildenafil; Tadalafil; Other (Specify); NR/NA

    - Dosage
    - Frequency
    - Duration
      - Administration (oral, inhaled, intravenous, subcutaneous)
  - Describe tests administered
  - Describe biomarkers
  - Describe echocardiographic tests
  - Describe co-treatments
  - Did the study use echocardiography and/or biomarkers?

    Echocardiography
    Biomarker(s)
    Echo + biomarkers
    NR/NA

IV. Outcomes Definitions

- Time points
  - Time 1
  - Time 2
  - Time 3
  - Time 4
  - Time 5
- Echocardiographic parameters (Check all that apply)
  - Right ventricle (RV) size (any RV linear dimension or area by 2D echo)
  - Right atrium (RA) size (any RA linear dimension or area by 2D echo)

    - Fractional area change (FAC)
    - Tricuspid Annular Plane Systolic Excursion (TAPSE)
    - Systolic excursion velocity (S-prime)
    - RIMP/MPI/Tei Index
    - Systolic pulmonary artery pressure (sPAP)
    - Mean pulmonary artery pressure (mPAP)
    - Tricuspid regurgitant (TR) jet velocity
    - Peak TR velocity
    - Right ventricular outflow tract (RVOT) velocity-time integral
    - Right ventricular ejection fraction (RVEF)
    - Pericardial effusion
    - Other (specify; don't need to include measures of LV function)
- Right-heart catheterization measures (Check all that apply)
    - Mean pulmonary artery pressure (mPAP)
    - Systolic pulmonary artery pressure (sPAP)
    - Diastolic pulmonary artery pressure (dPAP)
    - Pulmonary vascular resistance (PVR)
    - Cardiac output (CO)
    - Other right-heart catheterization measure (specify)
- Biomarkers (Check all that apply)
    - Natriuretic peptides (e.g., atrial natriuretic peptide, brain natriuretic peptide)
    - Endothelin-1
    - Uric acid
    - Troponin T
    - Nitric oxide
    - Asymmetric dimethylarginine
    - Cyclic guanosine monophosphate
    - D-dimer
    - Serotonin
    - Other biomarker (specify)
- Clinical outcomes (Check all that apply)
    - Diagnostic thinking efficacy
    - Therapeutic efficacy (e.g. clinician judgment about diagnosis/prognosis, choice of treatment)
    - Dyspnea
    - 6-minute walk change
    - 6-minute walk absolute score
    - Hospitalization
    - Functional class
    - Quality of life (e.g. SF-36, Minnesota Living With Heart Failure [MLWHF], Cambridge Pulmonary Hypertension Outcome Review [CAMPHOR])
    - Right ventricular dysfunction
    - Right heart failure
    - Mortality
    - Progression to right heart failure
    - Other clinical outcomes (specify)
    - Adverse effect – bleeding
    - Adverse effect – bruising
    - Adverse effect – infection
    - Adverse effect – transient ischemic attack from bubble/contrast echocardiogram
    - Adverse effect – liver function abnormalities

- Adverse effect – headache
- Adverse effect – flushing
- Adverse effect – cough
- Adverse effect – epistaxis
- Adverse effect – dyspepsia
- Adverse effect – diarrhea
- Adverse effect – peripheral edema
- Adverse effect – nausea
- Adverse effect – nasal congestion
- Adverse effect – dizziness
- Adverse effect – syncope
- Adverse effect – hypoxia
- Adverse effect – increased international normalized ratio
- Adverse effect – increased prothrombin time
- Adverse effect – line infection
- Adverse effect – site pain
- Adverse effect – abrupt catheter occlusion
- Adverse effect – other (specify)

- Comments

V. KQ 1 Outcomes

- Did the study present other clinical outcomes that will need to be extracted (i.e. bleeding, bruising, etc.)?
- Echo Parameter
  - RV size
  - RA size
  - Fractional area change
  - TAPSE
  - RIMP/MPI/Tei Index
  - sPAP (systolic pulmonary artery pressure)
  - mPAP (mean pulmonary artery pressure)
  - Tricuspid regurgitant jet velocity
  - Peak tricuspid regurgitant velocity
  - RVOT velocity-time integral
  - RVEF
  - Pericardial effusion
  - Echo Parameter Threshold
  - How was this measure calculated?
  - For how many patients was there no test result for this measure?
- Reference standard
  - mPAP (mean pulmonary artery pressure)-RH Cath
  - sPAP (systolic pulmonary artery pressure)-RH Cath
  - dPAP (diastolic pulmonary artery pressure)-RH Cath
  - PVR (pulmonary vascular resistance)-RH Cath
  - CO (cardiac output)-RH Cath
  - CI (cardiac Index)
  - RAP (right atrial pressure)
  - PCWP (pulmonary capillary wedge pressure)
  - Reference Standard Threshold
- Biomarker

Natriuretic peptides/BNP
Endothelin-1
Uric acid
Troponin T
Nitric oxide
Asymmetric dimethylarginine
Cyclic guanosine monophosphate
D-dimer

- How was this measure calculated?
- Biomarker Threshold
- For how many patients was there no test result for this measure?

- Data presentation
  - Dichotomous/ Continuous/ Both
  - If Dichotomous or Both selected:

    Echo Alone; Echo + Biomarkers; Biomarkers Alone
    - Test positive
      - Disease Positive – True positive N
      - Disease Negative – False positive N
      - Unclear – N unclear
      - Total – Total N
    - Test negative
      - Disease Positive – False negative
      - Disease Negative – True negative
      - Unclear – N unclear
      - Total – Total N
    - Test uncertain
      - Disease Positive – N positive
      - Disease Negative – N negative
      - Unclear – N unclear
      - Total – Total N
    - Total
      - Disease Positive – N positive
      - Disease Negative – N negative
      - Unclear – N unclear
      - Total – Total N
  - If Continuous or Both selected:

    Echo Alone; Echo + Biomarkers; Biomarkers Alone
    - Table 1
      - N for Analysis
      - Pearson product-moment correlation (r)
      - r^2
      - Bland-Altman analysis
      - Variability

        Standard Error(SE)/ Standard Deviation(SD)/ Other(Specify)
      - p-value between test and reference standard
      - Time interval between test and reference standard
    - Table 2
      - Disease Positive

        N Positive

Mean
- SD
- SE

Median
- IQR

- Disease Negative

N Negative
Mean
- SD
- SE

Median
- IQR

- Diagnosis Unclear

N Unclear
Mean
- SD
- SE

Median
- IQR

- Other

N
Mean
- SD
- SE

Median
- IQR

- p-value between Test and Reference Standard

VI. KQ 2 Outcomes

- Did the study report other clinical outcomes that will need to be abstracted?(Yes/No)
- Table 1, Table2, Table 3, Table 4, Table 5
  - Timing

    Baseline

    Intermediate term >30 days and ≤ 1 year
    - 1 month/ 2 months/ 3 months/ 4 months/ 6 months/ 1 year/ Other (Specify)

    Long-term > 1 year
    - 2 years/ 3 years/ 4 years/ 5 years/ Other (Specify)
  - Intervention

    Intervention 1
    - RV size
    - RA size
    - Fractional area change
    - TAPSE
    - RIMP/MPI/Tei Index
    - sPAP (systolic pulmonary artery pressure)
    - mPAP (mean pulmonary artery pressure)
    - Tricuspid regurgitant jet velocity
    - Peak tricuspid regurgitant velocity

- RVOT velocity-time integral
- RVEF
- Pericardial effusion
- RVSP
- Natriuretic peptides/BNP
- Endothelin-1
- Uric acid
- Troponin T
- Nitric oxide
- Asymmetric dimethylarginine
- Cyclic guanosine monophosphate
- D-dimer

Describe Intervention 1

Intervention 2

- RV size
- RA size
- Fractional area change
- TAPSE
- RIMP/MPI/Tei Index
- sPAP (systolic pulmonary artery pressure)
- mPAP (mean pulmonary artery pressure)
- Tricuspid regurgitant jet velocity
- Peak tricuspid regurgitant velocity
- RVOT velocity-time integral
- RVEF
- Pericardial effusion
- RVSP
- Natriuretic peptides/BNP
- Endothelin-1
- Uric acid
- Troponin T
- Nitric oxide
- Asymmetric dimethylarginine
- Cyclic guanosine monophosphate
- D-dimer
- NA

Describe Intervention 2

- Comparator

Comparator 1

- RV size
- RA size
- Fractional area change
- TAPSE
- RIMP/MPI/Tei Index
- sPAP (systolic pulmonary artery pressure)
- mPAP (mean pulmonary artery pressure)
- Tricuspid regurgitant jet velocity
- Peak tricuspid regurgitant velocity

- RVOT velocity-time integral
- RVEF
- Pericardial effusion
- RVSP
- Natriuretic peptides/BNP
- Endothelin-1
- Uric acid
- Troponin T
- Nitric oxide
- Asymmetric dimethylarginine
- Cyclic guanosine monophosphate
- D-dimer
- RH cath-mPAP
- RH cath-sPAP
- RH cath-dPAP
- RH cath-PVR
- RH cath-CO
- Cardiac index (CI)
- Right atrial pressure (RAP)
- Pulmonary capillary wedge pressure (PCWP)
- Dyspnea
- 6 minute walk change
- 6 minute walk (absolute)
- Hospitalization
- Functional class
- Quality of life
- Right ventricular dysfunction
- Right heart failure/progression to right heart failure
- Mortality
- Transplant
- Adverse effect – bleeding
- Adverse effect – bruising
- Adverse effect – infection
- Adverse effect – transient ischemic attack
- Adverse effect – liver function
- Adverse effect – headache
- Adverse effect – flushing
- Adverse effect – cough
- Adverse effect – epistaxis
- Adverse effect – dyspepsia
- Adverse effect – diarrhea
- Adverse effect – peripheral edema
- Adverse effect – nausea
- Adverse effect – nasal congestion
- Adverse effect – dizziness
- Adverse effect – syncope
- Adverse effect – hypoxia
- Adverse effect – increased INR

- Adverse effect – line infection
- Adverse effect – site pain
- Adverse effect – abrupt catheter occlusion
- Adverse effect – rash
- Adverse effect – jaw pain
- Composite outcome (Specify)

Describe Comparator 1

Comparator 2

- RV size
- RA size
- Fractional area change
- TAPSE
- RIMP/MPI/Tei Index
- sPAP (systolic pulmonary artery pressure)
- mPAP (mean pulmonary artery pressure)
- Tricuspid regurgitant jet velocity
- Peak tricuspid regurgitant velocity
- RVOT velocity-time integral
- RVEF
- Pericardial effusion
- RVSP
- Natriuretic peptides/BNP
- Endothelin-1
- Uric acid
- Troponin T
- Nitric oxide
- Asymmetric dimethylarginine
- Cyclic guanosine monophosphate
- D-dimer
- RH cath-mPAP
- RH cath-sPAP
- RH cath-dPAP
- RH cath-PVR
- RH cath-CO
- Cardiac index (CI)
- Right atrial pressure (RAP)
- Pulmonary capillary wedge pressure (PCWP)
- Dyspnea
- 6 minute walk change
- 6 minute walk (absolute)
- Hospitalization
- Functional class
- Quality of life
- Right ventricular dysfunction
- Right heart failure/progression to right heart failure
- Mortality
- Transplant
- Adverse effect – bleeding

- Adverse effect – bruising
- Adverse effect – infection
- Adverse effect – transient ischemic attack
- Adverse effect – liver function
- Adverse effect – headache
- Adverse effect – flushing
- Adverse effect – cough
- Adverse effect – epistaxis
- Adverse effect – dyspepsia
- Adverse effect – diarrhea
- Adverse effect – peripheral edema
- Adverse effect – nausea
- Adverse effect – nasal congestion
- Adverse effect – dizziness
- Adverse effect – syncope
- Adverse effect – hypoxia
- Adverse effect – increased INR
- Adverse effect – line infection
- Adverse effect – site pain
- Adverse effect – abrupt catheter occlusion
- Adverse effect – rash
- Adverse effect – jaw pain
- Composite outcome (Specify)

Describe Comparator 2

- Population and N for Analysis

  Intervention
  - Population
  - N for Analysis

  Comparator
  - Population
  - N for Analysis

- Result

  Mean
  Median
  Number Patients with Outcome
  % Patients w ith Outcome
  Relative Risk (RR)
  Relative Hazard (HR)
  Odds Ratio (OR)
  Risk difference
  Correlation
  Other (Specify)

- Variability

  Standard Error (SE)
  Standard Deviation (SD)
  Other (Specify)

- Confidence interval (CI) or Interquartile Range (IQR)

  95% CI/ Other % CI (Specify)/ IQR
  - LL (25% if IQR)

        - UL (75% if IQR)
    - p-value between treatment groups
- Describe the diagnostic thinking efficacy
- Describe the therapeutic efficacy
- Comments

VII. Clinical Outcomes

- Outcome reported on this form
    - Dyspnea
    - Six minute walk change
    - Six minute walk (absolute)
    - Hospitalization
    - Functional class
    - Quality of life (SF-36, MLWH, CAMPHOR)
    - Right ventricular dysfunction
    - Right heart failure/progression to right heart failure
    - Mortality
    - Transplant/progression to transplant
    - Adverse effect – bleeding
    - Adverse effect – bruising
    - Adverse effect – infection
    - Adverse effect – transient ischemic attack
    - Adverse effect – liver function abnormalities
    - Adverse effect – headache
    - Adverse effect – flushing
    - Adverse effect – cough
    - Adverse effect – epistaxis
    - Adverse effect – dyspepsia
    - Adverse effect – diarrhea
    - Adverse effect – peripheral edema
    - Adverse effect – nausea
    - Adverse effect – nasal congestion
    - Adverse effect – dizziness
    - Adverse effect – syncope
    - Adverse effect – hypoxia
    - Adverse effect – increased international normalized ratio
    - Adverse effect – line infection
    - Adverse effect – site pain
    - Adverse effect – abrupt catheter occlusion
    - Adverse effect – jaw pain
    - Adverse effect – rash
    - Composite outcome

        Composite outcome consisted of
    - RV size
    - RA size
    - Fractional area change
    - TAPSE
    - RIMP/MPI/Tei Index
    - sPAP
    - mPAP

- TR jet velocity
- Peak TR velocity/RVOT velocity-time interval
- RVEF
- Pericardial Effusion
- RVSP
- Natriuretic peptides/BNP
- Endothelin-1
- Uric acid
- Troponin T
- Nitric oxide
- Asymmetric dimethylarginine
- c-GMP
- D-dimer
- RH cath – sPAP
- RH cath – mPAP
- RH cath – dPAP
- RH cath –PVR
- RH cath – CO
- Cardiac Index (CI)
- Right atrial pressure (RAP)
- Pulmonary capillary wedge pressure (PCWP)

- Additional/alternate outcome name (if applicable)
- Authors' definition of outcome (if applicable)
- Table 1, 2, 3, 4, 5
  - Timing
    - Baseline
    - Intermediate term > 30 days and ≤ 1 year
      - 1 month/ 2 months/ 3 months/ 4 months/ 6 months/ 1 year/ Other (Specify)
    - Long-term > 1 year
      - 2 years/ 3 years/ 4 years/ 5 years/ Other (Specify)
  - Adjustments
    - Results are not adjusted
    - Age
    - Sex
    - Race/ethnicity
    - Comorbidity(ies) (Specify)
    - Body weight/ BMI
    - Risk factors
    - PAH classification
    - Other (specify all)
  - Group
    - Study Arm 1, 2, 3, 4
  - N for Analysis
  - Result
    - Mean
    - Median
    - Number Patients with Outcome
    - % Patients with Outcome
    - Relative Risk (RR)

Relative Hazard (HR)
Odds Ratio (OR)
Risk difference
Other (Specify)

- Variability
  - Standard Error (SE)
  - Standard Deviation (SD)
  - Other (Specify)
- Confidence Interval (CI) or Interquartile Range (IQR)
  - 95% CI/ Other % CI (Specify)/ IQR
    - LL (25% if IQR)
    - UL (75% if IQR)
- p-value between treatment groups
- Reference group (for comparisons between treatment groups)

- Comments

VIII. Quality

- Was this an accuracy study? (Yes/No)
  - If Yes:

    Population (P)
    - Was a consecutive or random sample of patients unrolled? (Yes/No/Unclear)
    - Was a case-control design avoided? (Yes/No/Unclear)
    - Did the study avoid inappropriate exclusions? (Yes/No/Unclear)
    - Could the selection of patients have introduced bias? (Yes/No/Unclear)

    Interventions (I)
    - Were the index test results interpreted without knowledge of the results of the reference standard? (Yes/No/Unclear)
    - If a threshold was used, was it pre-specified? (Yes/No/Unclear)
    - Could the conduct or interpretation of the index test have introduced bias? (Yes/No/Unclear)

    Comparators (C)
    - Is the reference standard likely to correctly classify the target condition? (Yes/No/Unclear)
    - Were the reference standard results interpreted without knowledge of the results of the index test? (Yes/No/Unclear)
    - Could the reference standard, its conduct, or its interpretation have introduced bias? (Yes/No/Unclear)

    Timing (T)
    - Was there an appropriate interval between index test(s) and reference standard? (Yes/No/Unclear)
    - Did all patients receive a reference standard? (Yes/No/Unclear)
    - Did all patients receive the same reference standard? (Yes/No/Unclear)
    - Were all patients included in the analysis? (Yes/No/Unclear)
    - Could the patient flow have introduced bias? (Yes/No/Unclear)

    Overall study rating (Good/Fair/Poor)
    - If Fair: Describe why the study was given a ‘Fair’ rating
    - If Poor: Describe why the study was given a ‘Poor’ rating
  - If No:

Was this study randomized? (Yes/No)

- If Yes:
  - Were study subjects randomized? (Yes/No/Unclear)
  - Was the randomization process described? (Yes/No/Unclear)
  - Was the outcome assessor blinded to study assignment? (Yes/No/Unclear)
  - Were patients blinded to study intervention? (Yes/No/Unclear)
  - Were results adjusted for clustering? (Yes/No/Unclear)
  - Were measures of outcomes based on validated procedures or instruments? (Yes/No/Unclear)
  - Conducted an intent-to-treat analysis? (Yes/No/Unclear)
  - Were all outcomes reported (i.e. was there evidence of selective outcome reporting)? (Yes/No/Unclear)
  - Were incomplete data adequately addressed? (Yes/No/Unclear)
  - Was there adequate power (either based on pre-study or post-hoc power calculations [80% power for primary outcome])? (Yes/No/Unclear)
  - Were systematic differences observed in baseline characteristics and prognostic factors across the groups compared? (Yes/No/Unclear)
  - Were comparable groups maintained? (Yes/No/Unclear)
  - Was there absence of potential important conflict-of-interest? (Yes/No/Unclear)
- If No:
  - Basic Design

    Is the study design prospective, retrospective, or mixed? (Prospective/Mixed/Retrospective/Cannot determine)
  - Selection Bias

    Inclusion/Exclusion Criteria
    - Are the inclusion/exclusion criteria clearly stated (does not require the reader to infer)? (Yes/Partially/No)
    - Did the study apply inclusion/exclusion criteria uniformly to all comparison groups? (Yes/Partially/No/NA)

    Recruitment
    - Did the strategy for recruiting participants into the study differ across study groups? (Yes/No/Cannot determine/NA)

    Baseline characteristics similar or appropriate adjusted analysis
    - Are key characteristics of study participants similar between intervention and control groups? If not similar, did the analysis appropriately adjust for important differences? (Yes/Partially/No/Insufficient reporting to be able to determine/NA)

    Comparison Group
    - Is the selection of the comparison group appropriate? (Yes/No/Cannot determine/NA)

- Performance Bias
  - Intervention implementation
    - What is the level of detail in describing the intervention or exposure?
      - High; very clear, all PI-required details provided
      - Medium; somewhat clear, majority of PI-required details provided
      - Low; unclear, many PI-required details missing
  - Concurrent/concomitant interventions
    - Did researchers isolate the impact from a concurrent intervention or unintended exposure that might bias the results, e.g., through multivariate analysis, stratification, or subgroup analysis? (Yes/Partially/Not described/NA)
- Attrition Bias
  - Equality of length of follow-up for participants
    - In cohort studies, is the length of follow-up different between the groups? (Yes/No or cannot determine/NA)
  - Completeness of follow-up
    - Was there a high rate of differential or overall attrition? (Yes/No/Cannot determine)
  - Attrition affecting participant composition
    - Did attrition result in a difference in group characteristics between baseline and follow-up? (Yes/No/Cannot determine)
  - Any attempt to balance
    - Any attempt to balance the allocation between the groups? (Yes/No/Cannot determine/NA)
  - Intention-to-treat analysis
    - Is the analysis conducted on an intention-to-treat (ITT) basis, that is, the intervention allocation status rather than the actual intervention received? (Yes/No/Cannot determine/NA)
- Detection Bias
  - Source of information re: outcomes
    - Are clinical outcomes (e.g. hemodynamic parameters, right heart failure or right ventricular dysfunction, and mortality) assessed using valid and reliable measures and implemented consistently across all study participants? (Yes/No/Cannot determine/NA)
    - Are patient-reported outcomes (e.g., symptom scores, quality of life) assessed using valid and reliable measures and implemented consistently across all study participants? (Yes/No/Cannot determine/NA)

        - Are functional capacity outcomes (e.g. 6-minute walk test, functional class) assessed using valid and reliable measures, implemented consistently across all study participants? (Yes/No/Cannot determine/NA)
    - Reporting Bias
        - Are any important primary outcomes missing from the results? (Yes/No/Cannot determine/Primary outcomes not pre-specified)
    - Other risk of bias issues
        - Are the statistical methods used to assess the primary outcomes appropriate to the data? (Yes/Partially/No/Cannot determine)
    - Power and sample size
        - Did the authors report conducting a power analysis or some other basis for determining the adequacy of study group sizes for the primary outcome(s) being abstracted? (Yes/No/NA)
    - Overall rating of the study (Good/Fair/Poor)

      If Fair: Describe why the study was given a 'Fair' rating

      If Poor: Describe why the study was given a 'Poor' rating

IX. Applicability

- Population (P)
    - Is there concern that the study population is inadequately described to assess the applicability of this study? (Yes/No)
    - Is there concern that participants are at widely differing points in natural history of disease? (Yes/No)
    - Is there concern that participants have widely differing degrees of disease severity? (Yes/No)
    - Is there concern that the included patients do not match the review question? (Yes/No)
    - Did the study exclude participants with other conditions that might be easily confused with PAH such as PH due to heart failure, thrombotic disease, COPD? (KQ1 only) (Yes/No)
    - Did the study include patients with a wide variety of conditions in addition to the target population? (Yes/No)
    - Did the study selectively recruit participants who demonstrated a history of favorable or unfavorable response to drug or other interventions for the condition? (KQ2 and KQ3 only) (Yes/No)
- Intervention (I)
    - Is there concern that the index test, its conduct, or interpretation differ from the review question? (KQ1,2) (Yes/No)
    - Is there concern that equipment or operator level of training/proficiency is not widely available? (KQ1, KQ2) (Yes/No)
    - Is there concern that the intervention (active arm) is not similar to that used in routine clinical practice? (Yes/No)
- Comparator (C)
    - Is there concern that the target condition as defined by the reference standard does not match the review question? (Yes/No)

- Outcomes (O)
    - Is there concern that cointerventions/treatments do not adequately reflect routine clinical practice? (Yes/No)
    - If surrogate outcomes were used, is there concern that they are not sufficiently clinically relevant? (Yes/No)
    - Is there concern that outcomes are not measured for sufficiently long duration of treatment? (KQ2, KQ3) (Yes/No)
    - Is there concern that potential adverse events associated with testing (KQ1,2) or treatment (KQ2,3) were not measured or reported? (Yes/No)
- Setting (S)
    - Is there concern that the care delivery setting is widely divergent from the current typical US setting? (Yes/No)
- Did the study have significant issues with applicability? (Yes/No)
- Comments

Appendix C. List of Included Studies

Ajami GH, Cheriki S, Amoozgar H, et al. Accuracy of doppler-derived estimation of pulmonary vascular resistance in congenital heart disease: An index of operability. Pediatr Cardiol. 2011;32(8):1168-1174. PMID: 21779967.

Allanore Y, Borderie D, Avouac J, et al. High N-terminal pro-brain natriuretic peptide levels and low diffusing capacity for carbon monoxide as independent predictors of the occurrence of precapillary pulmonary arterial hypertension in patients with systemic sclerosis. Arthritis Rheum. 2008;58(1):284-91. PMID: 18163505.

Andreassen AK, Wergeland R, Simonsen S, et al. N-terminal pro-B-type natriuretic peptide as an indicator of disease severity in a heterogeneous group of patients with chronic precapillary pulmonary hypertension. Am J Cardiol. 2006;98(4):525-9. PMID: 16893710.

Arcasoy SM, Christie JD, Ferrari VA, et al. Echocardiographic assessment of pulmonary hypertension in patients with advanced lung disease. Am J Respir Crit Care Med. 2003;167(5):735-40. PMID: 12480614.

Badesch DB, Bodin F, Channick RN, et al. Complete results of the first randomized, placebo-controlled study of bosentan, a dual endothelin receptor antagonist, in pulmonary arterial hypertension. Curr Ther Res Clin Exp. 2002;63(4):227-246.

Badesch DB, Feldman J, Keogh A, et al. ARIES-3: Ambrisentan Therapy in a Diverse Population of Patients with Pulmonary Hypertension. Cardiovasc Ther. 2011. PMID: 21884013.

Badesch DB, Feldman J, Keogh A, et al. ARIES-3: ambrisentan therapy in a diverse population of patients with pulmonary hypertension. Cardiovasc Ther. 2012;30(2):93-9. PMID: 21884013.

Badesch DB, Hill NS, Burgess G, et al. Sildenafil for pulmonary arterial hypertension associated with connective tissue disease. J Rheumatol. 2007;34(12):2417-22. PMID: 17985403.

Badesch DB, Tapson VF, McGoon MD, et al. Continuous intravenous epoprostenol for pulmonary hypertension due to the scleroderma spectrum of disease. A randomized, controlled trial. Ann Intern Med. 2000;132(6):425-34. PMID: 10733441.

Barst RJ, Ivy DD, Gaitan G, et al. A Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study of Oral Sildenafil Citrate in Treatment-Naive Children with Pulmonary Arterial Hypertension. Circulation. 2011. PMID: 22128226.

Barst RJ, Mubarak KK, Machado RF, et al. Exercise capacity and haemodynamics in patients with sickle cell disease with pulmonary hypertension treated with bosentan: results of the ASSET studies. Br J Haematol. 2010;149(3):426-35. PMID: 20175775.

Barst RJ, Oudiz RJ, Beardsworth A, et al. Tadalafil monotherapy and as add-on to background bosentan in patients with pulmonary arterial hypertension. J Heart Lung Transplant. 2011;30(6):632-43. PMID: 21256048.

Barst RJ, Rubin LJ, Long WA, et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. The Primary Pulmonary Hypertension Study Group. N Engl J Med. 1996;334(5):296-302. PMID: 8532025.

Barst RJ, Rubin LJ, McGoon MD, et al. Survival in primary pulmonary hypertension with long-term continuous intravenous prostacyclin. Ann Intern Med 1994;121(6):409-15. PMID: 8053614.

Bendayan D, Shitrit D, Ygla M, et al. Hyperuricemia as a prognostic factor in pulmonary arterial hypertension. Respir Med. 2003;97(2):130-3. PMID: 12587962.

Benza RL, Miller DP, Gomberg-Maitland M, et al. Predicting survival in pulmonary arterial hypertension: insights from the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL). Circulation. 2010;122(2):164-72. PMID: 20585012.

Bernus A, Wagner BD, Accurso F, et al. Brain natriuretic peptide levels in managing pediatric patients with pulmonary arterial hypertension. Chest. 2009;135(3):745-51. PMID: 18849405.

Bharani A, Patel A, Saraf J, et al. Efficacy and safety of PDE-5 inhibitor tadalafil in pulmonary arterial hypertension. Indian Heart J. 2007;59(4):323-8. PMID: 19126937.

Bogdan M, Humbert M, Francoual J, et al. Urinary cGMP concentrations in severe primary pulmonary hypertension. Thorax. 1998;53(12):1059-62. PMID: 10195079.

Bonderman D, Wexberg P, Martischnig AM, et al. A noninvasive algorithm to exclude pre-capillary pulmonary hypertension. Eur Respir J. 2011;37(5):1096-103. PMID: 20693249.

Borges AC, Knebel F, Eddicks S, et al. Right ventricular function assessed by two-dimensional strain and tissue Doppler echocardiography in patients with pulmonary arterial hypertension and effect of vasodilator therapy. Am J Cardiol. 2006;98(4):530-4. PMID: 16893711.

Brierre G, Blot-Souletie N, Degano B, et al. New echocardiographic prognostic factors for mortality in pulmonary arterial hypertension. Eur J Echocardiogr. 2010;11(6):516-22. PMID: 20185528.

Bustamante-Labarta M, Perrone S, De La Fuente RL, et al. Right atrial size and tricuspid regurgitation severity predict mortality or transplantation in primary pulmonary hypertension. J Am Soc Echocardiogr. 2002;15(10 Pt 2):1160-4. PMID: 12411899.

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Cavagna L, Caporali R, Klersy C, et al. Comparison of brain natriuretic peptide (BNP) and NT-proBNP in screening for pulmonary arterial hypertension in patients with systemic sclerosis. J Rheumatol. 2010;37(10):2064-70. PMID: 20634241.

Cella G, Vianello F, Cozzi F, et al. Effect of bosentan on plasma markers of endothelial cell activity in patients with secondary pulmonary hypertension related to connective tissue diseases. J Rheumatol. 2009;36(4):760-7. PMID: 19208592.

Cevik A, Kula S, Olgunturk R, et al. Quantitative Evaluation of Right Ventricle Function by Transthoracic Echocardiography in Childhood Congenital Heart Disease Patients with Pulmonary Hypertension. Echocardiography. 2012. PMID: 22494051.

Channick RN, Simonneau G, Sitbon O, et al. Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: a randomised placebo-controlled study. Lancet. 2001;358(9288):1119-23. PMID: 11597664.

Chin KM, Channick RN, Kim NH, et al. Central venous blood oxygen saturation monitoring in patients with chronic pulmonary arterial hypertension treated with continuous IV epoprostenol: correlation with measurements of hemodynamics and plasma brain natriuretic peptide levels. Chest. 2007;132(3):786-92. PMID: 17646224.

Ciurzynski M, Bienias P, Irzyk K, et al. Usefulness of echocardiography in the identification of an excessive increase in pulmonary arterial pressure in patients with systemic sclerosis. Kardiol Pol. 2011;69(1):9-15. PMID: 21267956.

Colle IO, Moreau R, Godinho E, et al. Diagnosis of portopulmonary hypertension in candidates for liver transplantation: a prospective study. Hepatology. 2003;37(2):401-9. PMID: 12540791.

Condliffe R, Radon M, Hurdman J, et al. CT pulmonary angiography combined with echocardiography in suspected systemic sclerosis-associated pulmonary arterial hypertension. Rheumatology (Oxford). 2011;50(8):1480-6. PMID: 21447566.

Dahiya A, Vollbon W, Jellis C, et al. Echocardiographic assessment of raised pulmonary vascular resistance: application to diagnosis and follow-up of pulmonary hypertension. Heart. 2010;96(24):2005-9. PMID: 21088122.

D'Alto M, Romeo E, Argiento P, et al. Bosentan-sildenafil association in patients with congenital heart disease-related pulmonary arterial hypertension and Eisenmenger physiology. Int J Cardiol. 2010. PMID: 21081251.

Denton CP, Cailes JB, Phillips GD, et al. Comparison of Doppler echocardiography and right heart catheterization to assess pulmonary hypertension in systemic sclerosis. Br J Rheumatol. 1997;36(2):239-43. PMID: 9133938.

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Galie N, Beghetti M, Gatzoulis MA, et al. Bosentan therapy in patients with Eisenmenger syndrome: A multicenter, double-blind, randomized, placebo-controlled study. Circulation. 2006;114(1):48-54. PMID: 16801459.

Galie N, Brundage BH, Ghofrani HA, et al. Tadalafil therapy for pulmonary arterial hypertension. Circulation. 2009;119(22):2894-903. PMID: 19470885.

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Grapsa I, Pavlopoulos H, Dawson D, et al. Retrospective study of pulmonary hypertensive patients: is right ventricular myocardial performance index a vital prognostic factor? Hellenic J Cardiol. 2007;48(3):152-60. PMID: 17629178.

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Study Groupings

Table C-1 presents a key to the primary and companion articles included in this report, organized alphabetically by study designation (if applicable). A full reference list follows the table.

Table C-1. Primary articles and companion articles

Study Designation	Primary Article	Companion Article(s)
AIR (Aerosolized Iloprost Randomized Study)	Olschewski, 2010[1]	None
ARIES-1 ARIES-2	Galie, 2008[2]	Oudiz 2009[3] Shapiro 2012[4]
ARIES-3	Badesch, 2012[5]	Badesch 2011[6]
ASSET-1 ASSET-2	Barst, 2010[7]	None
BREATH-1 (Bosentan Randomized Trial of Endothelin Antagonist Therapy)	Rubin, 2002[8]	Denton 2006[9] Galie 2003[10]
BREATHE-2 (Bosentan Randomized Trial of Endothelin Antagonist Therapy for PAH)	Humbert, 2004[11]	None
BREATHE-5 (Bosentan Randomized Trial of Endothelin Antagonist Therapy-5	Galie, 2006[12]	None
COMBI (Combination Therapy of Bosentan and aerosolized Iloprost in Idiopathic Pulmonary Arterial Hypertension trial)	Hoeper, 2006[13]	None
EARLY (Endothelin Antagonist Trial in Mildly Symptomatic Pulmonary Arterial Hypertension Patients)	Galie, 2008[14]	None
EVALUATION (Efficacy and Safety of Vardenafil in the Treatment of Pulmonary Arterial Hypertension Study)	Jing, 2011[15]	None
MSH (Multicenter Study of Hydroxyurea in Sickle Cell Anemia Patients)	Machado, 2006[16]	None
PACES (Pulmonary Arterial Hypertension Combination Study of Epoprostenol and Sildenafil)	Simonneau, 2008[17]	None
PHC (Pulmonary Hypertension Connection Registry)	Hampole, 2009[18]	None
PHIRST (Pulmonary Arterial Hypertension and Response to Tadalafil)	Galie, 2009[19]	Barst 2011[20] Oudiz 2012[21]
Primary Pulmonary Hypertension Study	Barst, 1996[22]	None
Prospective Evaluation of Adolescents and Children with Pulmonary Arterial Hypertension	Bernus, 2009[23]	None
REVEAL (Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management)	Benza, 2010[24] Farber, 2011[25]	None
SERAPH (Sildenafil versus Endothelin Receptor Antagonist for Pulmonary Hypertension Study)	Wilkins, 2005[26]	None
STARTS-1 (Sildenafil in Treatment-Naïve Children, Aged 1-17 Years, With Pulmonary Arterial Hypertension)	Barst, 2011[27]	None
SUPER (Sildenafil Use in Pulmonary Arterial Hypertension)	Galie, 2005[28]	Badesch 2007[29] Rubin 2011[30]
Treprostinil Study Group	McLaughlin, 2003[31] Simonneau, 2002[32]	None
TRIUMPH (TReprostinil Sodium Inhalation Used in the Management of Pulmonary Arterial Hypertension)	McLaughlin, 2010[33]	Frantz 2012[34]

Study Designation	Primary Article	Companion Article(s)
TRUST	Hiremath, 2010[35]	None
None indicated	Ajami, 2011[36]	None
None indicated	Allanore, 2008[37]	None
None indicated	Andreassen, 2006[38]	None
None indicated	Arcasoy, 2003[39]	None
None indicated	Badesch, 2000[40]	None
None indicated	Bendayan, 2003[41]	None
None indicated	Bharani, 2007[42]	None
None indicated	Bogdan, 1998[43]	None
None indicated	Bonderman, 2011[44]	None
None indicated	Borges, 2006[45]	None
None indicated	Brierre, 2010[46]	None
None indicated	Bustamante-Labarta, 2002[47]	None
None indicated	Campana, 2004[48]	None
None indicated	Cavagna, 2010[49]	None
None indicated	Cella, 2009[50]	None
None indicated	Cevik, 2012[51]	None
None indicated	Channick, 2001[52]	Badesch 2002[53]
None indicated	Chin, 2007[54]	None
None indicated	Ciurzynski, 2011[55]	None
None indicated	Colle, 2003[56]	None
None indicated	Condliffe, 2011[57]	None
None indicated	Dahiya, 2010[58]	None
None indicated	D'Alto, 2010[59]	None
None indicated	Denton, 1997[60]	None
None indicated	Dimitroulas, 2008[61]	None
None indicated	Dyer, 2006[62]	None
None indicated	Elstein, 2004[63]	None
None indicated	Fahmy Elnoamany, 2007[64]	None
None indicated	Feliciano, 2005[65]	None
None indicated	Fijalkowska, 2006[66]	None
None indicated	Filusch, 2010[67]	None
None indicated	Fisher, 2009[68]	None
None indicated	Fitzgerald, 2012[69]	None
None indicated	Fix, 2007[70]	None
None indicated	Fonseca, 2012[71]	None
None indicated	Forfia, 2006[72]	None
None indicated	Frea, 2011[73]	None
None indicated	Friedberg, 2006[74]	None
None indicated	Fukuda, 2011[75]	None
None indicated	Gan, 2006[76]	None
None indicated	Ghio, 2010[77]	None
None indicated	Ghio, 2004[78]	None
None indicated	Ghofrani, 2002[79]	None
None indicated	Gialafos, 2008[80]	None
None indicated	Goto, 2010[81]	None
None indicated	Grapsa, 2007[82]	None
None indicated	Grubstein, 2008[83]	None
None indicated	Hachulla, 2005[84]	None
None indicated	Haddad, 2009[85]	None
None indicated	Halank, 2011[86]	None
None indicated	Hammerstingl, 2012[87]	None
None indicated	Heresi, 2010[88]	None
None indicated	Heresi, 2012[89]	None
None indicated	Higenbottam, 1993[90]	None
None indicated	Hinderliter, 1997[91]	None
None indicated	Hiramoto, 2009[92]	None

Study Designation	Primary Article	Companion Article(s)
None indicated	Ho, 2009[93]	None
None indicated	Hoeper, 2007[94]	None
None indicated	Homma, 2001[95]	None
None indicated	Hsu, 2008[96]	None
None indicated	Hua, 2009[97]	None
None indicated	Jacobs, 2009[98]	None
None indicated	Jansa, 2012[99]	None
None indicated	Kaya, 2012[100]	None
None indicated	Kemp, 2012[101]	None
None indicated	Keogh, 2011[102]	None
None indicated	Knirsch, 2011[103]	None
None indicated	Kopec, 2012[104]	None
None indicated	Kovacs, 2010[105]	None
None indicated	Lammers, 2009[106]	None
None indicated	Langleben, 1999[107]	None
None indicated	Leuchte, 2005[108]	None
None indicated	Lindqvist, 2011[109]	None
None indicated	Lorenzen, 2011[110]	None
None indicated	Low, 2011[111]	None
None indicated	Machado, 2004[112]	None
None indicated	Mahapatra, 2006[113]	None
None indicated	Mathai, 2011[114]	None
None indicated	Mauritz, 2011[115]	None
None indicated	McLaughlin, 2006[116]	None
None indicated	McLean, 2007[117]	None
None indicated	Michelakis, 2002[118]	None
None indicated	Minniti, 2009[119]	None
None indicated	Montani, 2007[120]	None
None indicated	Morishita, 2009[121]	None
None indicated	Mourani, 2008[122]	None
None indicated	Mukherjee, 2004[123]	None
None indicated	Mukherjee, 2003[124]	None
None indicated	Mukhopadhyay, 2011[125]	None
None indicated	Murata, 1997[126]	None
None indicated	Nagaya, 2000[127]	None
None indicated	Nakayama, 2007[128]	None
None indicated	Nakayama, 1998[129]	None
None indicated	Nath, 2005[130]	None
None indicated	Nickel, 2012[131]	None
None indicated	Nickel, 2008[132]	None
None indicated	Njaman, 2007[133]	None
None indicated	Nogami, 2009[134]	None
None indicated	Ogawa, 2012[135]	None
None indicated	Olschewski, 2002[136]	None
None indicated	Park, 2004[137]	None
None indicated	Phung, 2009[138]	None
None indicated	Pilatis, 2000[139]	None
None indicated	Pyxaras, 2011[140]	None
None indicated	Rajagopalan, 2009[141]	Rajagopalan 2007[142]
None indicated	Rajaram, 2012[143]	None
None indicated	Raymond, 2002[144]	None
None indicated	Reichenberger, 2011[145]	None
None indicated	Rhodes, 2011[146]	None
None indicated	Rich, 2012[147]	None
None indicated	Rich, 2011[148]	None
None indicated	Roeleveld, 2005[149]	None
None indicated	Roule, 2010[150]	None

Study Designation	Primary Article	Companion Article(s)
None indicated	Ruan, 2007[151]	None
None indicated	Rubin, 1990[152]	Barst, 1994[153]
None indicated	Ruiz-Irastorza, 2012[154]	None
None indicated	Sadushi-Kolici, 2012[155]	None
None indicated	Sanli, 2012[156]	None
None indicated	Sastry, 2007[157]	None
None indicated	Schumann, 2010[158]	None
None indicated	Sebbag, 2001[159]	None
None indicated	Selby, 2012[160]	None
None indicated	Selimovic, 2007[161]	None
None indicated	Shimony, 2012[162]	None
None indicated	Simeoni, 2008[163]	None
None indicated	Soon, 2011[164]	None
None indicated	Souza, 2007[165]	None
None indicated	Steen, 2008[166]	None
None indicated	Taguchi, 2012[167]	None
None indicated	Takatsuki, 2012[168]	None
None indicated	Takatsuki, 2012[169]	None
None indicated	Takatsuki, 2012[170]	None
None indicated	Takatsuki, 2012[171]	None
None indicated	Takeda, 2010[172]	None
None indicated	Tei, 1996[173]	None
None indicated	Thakkar, 2012[174]	None
None indicated	Tian, 2011[175]	None
None indicated	Torbicki, 2003[176]	None
None indicated	Torregrosa, 2001[177]	None
None indicated	Toyono, 2008[178]	None
None indicated	Tutar, 1999[179]	None
None indicated	Utsunomiya, 2009[180]	None
None indicated	Utsunomiya, 2011[181]	None
None indicated	van Albada, 2008[182]	None
None indicated	Vizza, 2012[183]	None
None indicated	Vizza, 2008[184]	None
None indicated	Vlahos, 2008[185]	None
None indicate	Voelkel, 2000[186]	None
None indicated	Vonk, 2007[187]	None
None indicated	Willens, 2008[188]	None
None indicated	Williams, 2006[189]	None
None indicated	Yamada, 2012[190]	None
None indicated	Yanagisawa, 2012[191]	None
None indicated	Yang, 2012[192]	None
None indicated	Yoshida, 2012[193]	None
None indicated	Zafrir, 2007[194]	None
None indicated	Zeng, 2011[195]	None
None indicated	Zeng, 2011[196]	None
None indicated	Zhao, 2012[197]	None

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Appendix D. Quality and Applicability of Included Studies

Table D-1. Quality and applicability for KQ 1 studies

Study	Test Measures	Quality	Limitations to Applicability
Ajami, 2011[1]	• TRV/VTIRVOT	Good	• Participants had widely differing degrees of disease severity • Included patients did not match the review question • Study excluded participants with other conditions that might be easily confused with PAH such as PH due to heart failure, thrombotic disease, COPD
Allanore, 2008[2]	• NT-proBNP, plasma • sPAP	Good	• Included patients did not match the review question • Study excluded participants with other conditions that might be easily confused with PAH such as PH due to heart failure, thrombotic disease, COPD • Index test, its conduct, or interpretation differed from the review question
Arcasoy 2003[3]	• sPAP • RAP	Good	• Study population is inadequately described • Included patients did not match the review question • Study included patients with a wide variety of conditions in addition to the target population
Bogdan, 1998[4]	• cGMP, urine	Poor	• Participants were at widely differing points in natural history of disease • Participants had widely differing degrees of disease severity • Included patients did not match the review question • Study excluded participants with other conditions that might be easily confused with PAH such as PH due to heart failure, thrombotic disease, COPD • Study included patients with a wide variety of conditions in addition to the target population
Bonderman, 2011[5]	• NT-proBNP • sPAP • RA size • RV size • TAPSE	Good	• Included patients did not match the review question
Cavagna, 2010[6]	• BNP • NT-proBNP	Good	• Study excluded participants with other conditions that might be easily confused with PAH such as PH due to heart failure, thrombotic disease, COPD • None

Study	Test Measures	Quality	Limitations to Applicability
Cevik, 2012[7]	• RIMP/MPI/Tei index • mPAP • S' • TAPSE • TRV/VTI_{RVOT}	Fair	• Study population is inadequately described • Study excluded participants with other conditions that might be easily confused with PAH such as PH due to heart failure, thrombotic disease, COPD • Care delivery setting is widely divergent from typical U.S. setting
Ciurzynski, 2011[8]	• Transtricuspid gradient rest/exercise	Good	• None
Colle, 2003[9]	• sPAP	Good	• None
Condliffe, 2011[10]	• Tricuspid gradient	Fair	• None
Dahiya, 2010[11]	• TRV/VTIRVOT	Good	• Participants were at widely differing points in natural history of disease • Participants had widely differing degrees of disease severity
Denton, 1997[12]	• RV size • sPAP	Fair	• None
Farber, 2011[13]	• sPAP • RAP	Fair	• None
Fisher, 2009[14]	• sPAP • Transtricuspid gradient	Good	• Study excluded participants with other conditions that might be easily confused with PAH such as PH due to heart failure, thrombotic disease, COPD
Fitzgerald, 2012[15]	• TRV • mPAP	Poor	• Study population is inadequately described • Participants were at widely differing points in natural history of disease • Participants had widely differing degrees of disease severity • Included patients did not match the review question • Index test, its conduct, or interpretation differed from the review question • Cointerventions/treatments did not adequately reflect routine clinical practice
Fonseca, 2011[16]	• TRV • Uric acid	Fair	• None
Frea, 2011[17]	• NT-proBNP • FAC • RIMP/MPI/Tei index • RV size • TRV/VTIRVOT • TAPSE	Fair	• Index test, its conduct, or interpretation differed from the review question
Fukuda, 2011[18]	• FAC • TAPSE • RIMP/MPI/Tei index • sPAP	Fair	• Participants had widely differing degrees of disease severity • Included patients did not match the review question • Study excluded participants with other conditions that might be easily confused with PAH such as PH due to heart failure, thrombotic disease, COPD
Ghio, 2004[19]	• NT-proBNP	Fair	• Target condition as defined by the reference standard did not match the review question
Gialafos, 2008[20]	• NT-proBNP • RIMP/MPI/Tei index	Fair	• None

Study	Test Measures	Quality	Limitations to Applicability
Hachulla, 2005[21]	• TRV	Poor	• None
Hammerstingl, 2012[22]	• sPAP • mPAP	Fair	• Participants were at widely differing points in natural history of disease • Participants had widely differing degrees of disease severity • Included patients did not match the review question • Study included patients with a wide variety of conditions in addition to the target population • Index test, its conduct, or interpretation differed from the review question • Equipment or operator level of training/proficiency is not widely available • Intervention (active arm) was not similar to that used in routine clinical practice
Hsu, 2008[23]	• sPAP	Good	• None
Hua, 2009[24]	• sPAP	Good	• None
Jansa, 2012[25]	• TRV	Fair	• Participants were at widely differing points in natural history of disease • Participants had widely differing degrees of disease severity
Kovacs, 2010[26]	• sPAP rest and exercise	Good	• None
Lindqvist, 2011[27]	• TRV/VTIRVOT	Fair	• Participants had widely differing degrees of disease severity • Included patients did not match the review question
Low, 2011[28]	• Transtricuspid gradient	Poor	• Participants were at widely differing points in natural history of disease • Participants had widely differing degrees of disease severity • Included patients did not match the review question
Machado, 2006[29]	• NT-proBNP	Poor	• None
McLean, 2007[30]	• RV end-diastolic diameter (RVD) • Tpeak (RV tricuspid annular motion by TDI, time from beginning of IC to first Sm peak)	Poor	• Participants were at widely differing points in natural history of disease • Participants had widely differing degrees of disease severity • Included patients did not match the review question • Study included patients with a wide variety of conditions in addition to the target population • Index test, its conduct, or interpretation differed from the review question • Intervention (active arm) was not similar to that used in routine clinical practice • Cointerventions/treatments did not adequately reflect routine clinical practice
Mourani, 2008[31]	• RA size • RV size • Transtricuspid gradient	Fair	• Participants were at widely differing points in natural history of disease • Participants had widely differing degrees of disease severity • Included patients did not match the review question • Study excluded participants with other conditions that might be easily confused with PAH such as PH due to heart failure, thrombotic disease, COPD • Study included patients with a wide variety of conditions in addition to the target population

Study	Test Measures	Quality	Limitations to Applicability
Mukerjee, 2004[32]	• sPAP	Fair	• Index test, its conduct, or interpretation differed from the review question • Potential adverse events associated with testing or treatment were not measured or reported
Murata, 1997[33]	• sPAP	Fair	• Included patients did not match the review question • Study excluded participants with other conditions that might be easily confused with PAH such as PH due to heart failure, thrombotic disease, COPD
Nakayama, 1998[34]	• sPAP • mPAP	Fair	• Included patients did not match the review question • Study excluded participants with other conditions that might be easily confused with PAH such as PH due to heart failure, thrombotic disease, COPD • Potential adverse events associated with testing or treatment were not measured or reported
Nogami, 2009[35]	• sPAP	Good	• Participants had widely differing degrees of disease severity • Included patients did not match the review question • Study included patients with a wide variety of conditions in addition to the target population
Phung, 2009[36]	• sPAP	Good	• Study included patients with a wide variety of conditions in addition to the target population
Pilatis, 2000[37]	• RV size • sPAP	Fair	• Target condition as defined by the reference standard did not match the review question • Potential adverse events associated with testing or treatment were not measured or reported
Rajagopalan, 2009[38] Rajagopalan, 2007[39]	• TRV/VTIRVOT • sPAP • S’	Fair	• Participants were at widely differing points in natural history of disease • Participants had widely differing degrees of disease severity • Included patients did not match the review question • Study excluded participants with other conditions that might be easily confused with PAH such as PH due to heart failure, thrombotic disease, COPD • Study included patients with a wide variety of conditions in addition to the target population
Rajaram, 2012[40]	• sPAP • mPAP • Pericardial effusion	Fair	• None
Rich, 2011[41]	• sPAP	Good	• Included patients did not match the review question • Study excluded participants with other conditions that might be easily confused with PAH such as PH due to heart failure, thrombotic disease, COPD • Index test, its conduct, or interpretation differed from the review question

Study	Test Measures	Quality	Limitations to Applicability
Roeleveld, 2005[42]	• sPAP	Fair	• Included patients did not match the review question • Study excluded participants with other conditions that might be easily confused with PAH such as PH due to heart failure, thrombotic disease, COPD
Roule, 2010[43]	• TRV • TRV/VTIRVOT	Good	• Study excluded participants with other conditions that might be easily confused with PAH such as PH due to heart failure, thrombotic disease, COPD
Ruan, 2007[44]	• FAC • RV size • sPAP	Fair	• Participants were at widely differing points in natural history of disease • Participants had widely differing degrees of disease severity • Included patients did not match the review question • Study excluded participants with other conditions that might be easily confused with PAH such as PH due to heart failure, thrombotic disease, COPD
Ruiz-Irastorza, 2012[45]	• sPAP • mPAP	Fair	• Participants were at widely differing points in natural history of disease • Participants had widely differing degrees of disease severity • Study included patients with a wide variety of conditions in addition to the target population
Sanli, 2012[46]	• RV size • mPAP • Nitric oxide • RIMP/MPI/Tei index • TAPSE	Fair	• Study population is inadequately described • Participants were at widely differing points in natural history of disease • Participants had widely differing degrees of disease severity • Study included patients with a wide variety of conditions in addition to the target population
Selby, 2012[47]	• sPAP	Fair	• Study population is inadequately described
Selimovic, 2007[48]	• sPAP • mPAP	Good	• Included patients did not match the review question • Study excluded participants with other conditions that might be easily confused with PAH such as PH due to heart failure, thrombotic disease, COPD
Simeoni, 2008[49]	• NT-proBNP	Poor	• Participants were at widely differing points in natural history of disease • Participants had widely differing degrees of disease severity • Included patients did not match the review question • Study excluded participants with other conditions that might be easily confused with PAH such as PH due to heart failure, thrombotic disease, COPD • Study included patients with a wide variety of conditions in addition to the target population
Steen, 2008[50]	• sPAP rest/exercise	Fair	• Target condition as defined by the reference standard did not match the review question • Surrogate outcomes were not sufficiently clinically relevant

Study	Test Measures	Quality	Limitations to Applicability
Takatsuki, 2012[51]	• S' • mPAP	Fair	• Study population is inadequately described • Participants were at widely differing points in natural history of disease • Participants had widely differing degrees of disease severity • Study excluded participants with other conditions that might be easily confused with PAH such as PH due to heart failure, thrombotic disease, COPD
Tei, 1996[52]	• RIMP/MPI/Tei index	Poor	• Participants were at widely differing points in natural history of disease • Participants had widely differing degrees of disease severity • Included patients did not match the review question • Study excluded participants with other conditions that might be easily confused with PAH such as PH due to heart failure, thrombotic disease, COPD
Tian, 2011[53]	• sPAP • mPAP	Fair	• Included patients did not match the review question • Study excluded participants with other conditions that might be easily confused with PAH such as PH due to heart failure, thrombotic disease, COPD
Thakkar, 2012[54]	• sPAP • NT-proBNP	Fair	• Participants were at widely differing points in natural history of disease • Participants had widely differing degrees of disease severity • Included patients did not match the review question • Study excluded participants with other conditions that might be easily confused with PAH such as PH due to heart failure, thrombotic disease, COPD • Study included patients with a wide variety of conditions in addition to the target population
Torregrosa, 2001[55]	• sPAP	Fair	• None
Toyono, 2008[56]	• BNP	Good	• Participants were at widely differing points in natural history of disease • Participants had widely differing degrees of disease severity
Tutar, 1999[57]	• Endothelin-1, plasma	Fair	• Participants had widely differing degrees of disease severity
Vlahos, 2007[58]	• TRV/VTIRVOT	Poor	• Included patients did not match the review question • Study excluded participants with other conditions that might be easily confused with PAH such as PH due to heart failure, thrombotic disease, COPD
Vonk, 2007[59]	• RIMP/MPI/Tei index • sPAP	Fair	• None
Willens, 2008[60]	• sPAP	Fair	• Included patients did not match the review question
Williams, 2006[61]	• NT-proBNP	Fair	• None

Abbreviations: BNP=brain natriuretic peptide; cGMP= cyclic guanosine monophosphate; CHF=congestive heart failure; COPD=chronic obstructive pulmonary disease; CTEPH=chronic thromboembolic pulmonary hypertension; CVD=collagen vascular disease; DLCO=diffusion capacity of the lung for carbon monoxide; FAC=fractional area change; mPAP=mean pulmonary artery pressure; MPI=myocardial performance index; NT-proBNP=N-terminal pro-B-type natriuretic peptide; NYHA=New York Heart Association; PAH=pulmonary arterial hypertension; PH=pulmonary hypertension; PPH=primary pulmonary hypertension; PVR=pulmonary vascular resistance; RA=right atrium; RHC=right heart catheterization; RIMP=right index of myocardial performance; RV=right ventricle; S'=tricuspid lateral annular systolic velocity; sPAP=systolic pulmonary artery

pressure; SSc=systemic sclerosis; TAPSE=tricuspid annular plane systolic excursion; TDI=tissue Doppler imaging; TRV=tricuspid regurgitant jet velocity; VSD=ventricular septal defect; VTI_{RVOT}=velocity-time integral of right ventricular outflow tract

Table D-2. Quality and applicability for KQ 2 studies

Study	Index Tests/Comparators	Quality	Limitations to Applicability
Andreassen, 2006[62]	• BNP • Cardiac index • Functional class • RHC-mPAP • RHC-PVR • RHC-sPAP • RAP • Mortality	Good	• None
Badesch, 2012[63] Badesch 2011[64]	• BNP	Good	• Included patients did not match the review question
Barst, 1996[65]	• mPAP	Good	• None
Bendayan, 2002[66]	• Uric acid • 6MWD (absolute) • Functional class • Mortality • RHC-CO • RHC-mPAP	Good	• None
Benza, 2010[67]	• BNP >180 • BNP<50 • Pericardial effusion • Mortality	Good	• None
Bernus, 2009[68]	• BNP • Cardiac index • Peak TRV • PCWP • RHC-mPAP • RHC-PVR • Right atrial pressure • RV size • TRV	Good	• None
Bharani, 2007[69]	• sPAP	Fair	• Intervention (active arm) was not similar to that used in routine clinical practice

Study	Index Tests/Comparators	Quality	Limitations to Applicability
Borges, 2006[70]	• RIMP/MPI/Tei index • RV size • 6MWD (absolute) • RHC-PVR	Good	• None
Brierre, 2010[71]	• mPAP • mPAP >= 49 • Pericardial effusion • RIMP/MPI/Tei index • RIMP/MPI/Tei index ≥0.98 • TAPSE • Mortality	Good	• Outcomes were not measured for sufficiently long duration of treatment
Bustamante-Labarta, 2002[72]	• RA size • Survival free from lung transplant	Good	• None
Campana, 2004[73]	• BNP • Cardiac index • FAC • RV size • TAPSE • mPAP • Right atrial pressure • RVEF	Good	• None
Cella, 2009[74]	• RVSP • Nitric oxide • 6MWD (change)	Good	• None
Channick, 2001[75] Badesch 2002[76]	• mPAP	Good	• Potential adverse events associated with testing or treatment were not measured or reported
Chin, 2007[77]	• BNP • 6MWD (absolute) • PCWP • RHC-CO • RHC-mPAP • RHC-PVR • Right atrial pressure	Good	• None
Dimitroulas, 2007[78]	• BNP	Good	• None
D'Alto, 2010[79]	• BNP	Fair	• None
Dyer, 2006[80]	• RIMP/MPI/Tei index • RHC-mPAP	Fair	• None
Elstein, 2004[81]	• BNP • Tricuspid insufficiency	Good	• None

Study	Index Tests/Comparators	Quality	Limitations to Applicability
Fahmy Elnoamany, 2007[82]	• Endothelin-1 • sPAP • RHC-sPAP • RIMP/MPI/Tei Index • RVEF	Fair	• None
Feliciano, 2005[83]	• RIMP/MPI/Tei index	Good	• None
Fijalkowska, 2006[84]	• BNP • FAC • Pericardial effusion • RA size • RIMP/MPI/Tei index • RV size • Troponin T • 6MWD (absolute) • Cardiac index • Functional class • Peak TRV • RHC-mPAP • RHC-PVR • Right atrial pressure • Mortality	Good	• None
Filusch, 2010[85]	• cTroponin T • hsTroponin T • BNP • Mortality • WHO class	Good	• Surrogate outcomes were not sufficiently clinically relevant
Forfia, 2006[86]	• TAPSE • RHC-PVR • Mortality	Good	• None
Friedberg, 2006[87]	• mPAP • BNP • sPAP • RHC-mPAP • RHC-sPAP	Good	• Included patients did not match the review question • Study included patients with a wide variety of conditions in addition to the target population
Galie, 2008[88] Oudiz 2009[89] Shapiro 2012[90]	• BNP	Good	• None

Study	Index Tests/Comparators	Quality	Limitations to Applicability
Gan, 2006[91]	• BNP • 6MWD (absolute) • Cardiac index • RHC-mPAP • RHC-PVR • Right atrial pressure • RVEF	Good	• None
Ghio, 2010[92]	• FAC • Pericardial effusion • RIMP/MPI/Tei index • sPAP • TAPSE • Mortality	Good	• Study population was inadequately described to assess the applicability of this study • Target condition as defined by the reference standard did not match the review question
Ghofrani, 2002[93]	• BNP • cGMP • RHC-PVR	Fair	• Surrogate outcomes were not sufficiently clinically relevant •
Goto, 2010[94]	• BNP • sPAP • RHC-mPAP • RHC-sPAP	Good	• Study population was inadequately described to assess the applicability of this study • Participants had widely differing degrees of disease severity • Included patients did not match the review question
Grapsa, 2007[95]	• RIMP/MPI/Tei index • Pericardial effusion • RA size • TRV	Good	• None
Grubstein, 2008[96]	• sPAP • RHC-sPAP	Fair	• None
Haddad, 2009[97]	• mPAP • sPAP • RHC-mPAP • RHC-sPAP	Good	• None
Halank, 2011[98]	• BNP • Median	Fair	• None
Hampole, 2009[99]	• BNP • Mortality	Good	• None
Heresi, 2012[100]	• cTnI (detectable vs. nondetectable) • BNP • NYHA class • RA size • 6MWD	Good	• None

Study	Index Tests/Comparators	Quality	Limitations to Applicability
Heresi, 2010[101]	• BNP • 6MWD (absolute) • Cardiac index • RHC-mPAP • RHC-PVR • Right atrial pressure • Mortality	Good	• None
Hinderliter, 1997[102]	• FAC • Pericardial effusion • RV size • sPAP • TRV • 6MWD (absolute) • Cardiac index • RHC-mPAP • Right atrial pressure • RHC-sPAP	Fair	• Outcomes were not measured for sufficiently long duration of treatment • Potential adverse events associated with testing or treatment were not measured or reported
Hiramoto, 2009[103]	• BNP • Endothelin-1	Fair	• None
Ho, 2009[104]	• RIMP/MPI/Tei Index • FAC • BNP • sPAP • RVEF	Good	• None
Homma, 2001[105]	• sPAP • RHC-sPAP	Good	• None
Jacobs, 2009[106]	• BNP	Fair	• None
Kaya, 2012[107]	• RV size • RA size • sPAP • S’	Good	• None
Keogh, 2011[108]	• sPAP	Fair	• None
Knirsch, 2011[109]	• BNP	Good	• Study population was inadequately described to assess the applicability of this study • Study included patients with a wide variety of conditions in addition to the target population • Cointerventions/treatments did not adequately reflect routine clinical practice • Outcomes were not measured for sufficiently long duration of treatment
Kopec, 2012[110]	• BNP • ET-1	Fair	• Index test, its conduct, or interpretation differed from the review question

Study	Index Tests/Comparators	Quality	Limitations to Applicability
Lammers, 2009[111]	• BNP • 6MWD (absolute) • Functional class	Good	• None
Langleben, 1999[112]	• Endothelin-1	Good	• None
Leuchte, 2005[113]	• Change in BNP • BNP • Change in : • 6MWD (absolute) • Cardiac index • RHC-CO • RHC-mPAP • RHC-PVR • Right atrial pressure	Good	• None
Lorenzen, 2011[114]	• BNP • Uric acid • Mortality	Good	• None
Machado, 2006[29]	• BNP • BNP ≥160, unadjusted ≥160, adjusted log10, adjusted log10, unadjusted • 6MWD (absolute) • mPAP • PCWP • RA size • RHC-CO • RHC-dPAP • RHC-PVR • RHC-sPAP • RV size • TRV • Mortality	Poor	• None
Machado, 2004[115]	• Nitric oxide • sPAP • mPAP • RHC-sPAP	Fair	• None
Mahapatra, 2006[116]	• RIMP/MPI/Tei Index • RVSP • Mortality	Fair	• None

Study	Index Tests/Comparators	Quality	Limitations to Applicability
Mathai, 2011[117]	• FAC • Peak TRV • Pericardial effusion • RA size • TAPSE • Mortality	Fair	• None
Mauritz, 2011[118]	• BNP	Good	• None
McLaughlin, 2010[119] Frantz, 2012[120]	• BNP	Good	• None
Michelakis, 2002[121]	• cGMP	Fair	• Surrogate outcomes were not sufficiently clinically relevant • Outcomes were not measured for sufficiently long duration of treatment • Potential adverse events associated with testing or treatment were not measured or reported
Minniti, 2009[122]	• BNP • TRV	Poor	• None
Montani, 2007[123]	• Endothelin-1 • Cardiac index • RHC-PVR • Right atrial pressure	Fair	• Participants were at widely differing points in natural history of disease • Intervention (active arm) was not similar to that used in routine clinical practice
Morishita, 2009[124]	• Pericardial effusion • RA size • RA size • BNP • Functional class	Good	• None
Mukerjee, 2003[125]	• BNP • RHC-mPAP • RHC-PVR	Good	• None
Nagaya, 2000[126]	• ANP • BNP • PCWP • RHC-CO • RHC-mPAP • Right atrial pressure • Mortality • RHC-PVR • Right atrial pressure • RV size	Good	• None
Nakayama, 2007[127]	• BNP	Fair	• None

Study	Index Tests/Comparators	Quality	Limitations to Applicability
Nath, 2005[128]	• Peak TRV • RIMP/MPI/Tei Index • RV size • sPAP • TRV • Functional class	Good	• Participants were at widely differing points in natural history of disease • Participants had widely differing degrees of disease severity
Nickel, 2012[129]	• BNP • Uric acid • Mortality	Fair	• None
Nickel, 2008[130]	• BNP • Uric acid • Composite outcome (death or lung transplantation)	Fair	• Participants were at widely differing points in natural history of disease • Participants had widely differing degrees of disease severity
Njaman, 2007[131]	• Uric acid • Mortality	Good	• None
Ogawa, 2012[132]	• BNP	Fair	• None
Park, 2004[133]	• sPAP • BNP • Clinical event	Fair	• None
Pyxaras, 2011[134]	• sPAP • mPAP • RHC-sPAP • RHC-mPAP	Good	• None
Raymond, 2002[135]	• FAC • Peak TRV • Pericardial effusion • RA size • Mortality • Composite outcome (death or transplantation)	Fair	• None
Rhodes, 2011[136]	• BNP • 6MWD (absolute) • Cardiac index • PCWP • RHC-PVR • Right atrial pressure • Mortality	Good	• Participants were at widely differing points in natural history of disease • Participants had widely differing degrees of disease severity
Sadushi-Kolici, 2012[137]	• Pericardial effusion • Mortality	Fair	• None
Schumann, 2010[138]	• BNP • sPAP	Good	• Participants were at widely differing points in natural history of disease • Participants had widely differing degrees of disease severity

Study	Index Tests/Comparators	Quality	Limitations to Applicability
Sebbag, 2001[139]	• RIMP/MPI/Tei Index • SPAP	Good	• Participants were at widely differing points in natural history of disease • Participants had widely differing degrees of disease severity • Potential adverse events associated with testing or treatment were not measured or reported
Shimony, 2012[140]	• Pericardial effusion (prevalent v incident) • Mortality	Fair	• None
Simeoni, 2008[49]	• BNP	Good	• Participants were at widely differing points in natural history of disease • Participants had widely differing degrees of disease severity • Included patients did not match the review question • Study excluded participants with other conditions that might be easily confused with PAH such as PH due to heart failure, thrombotic disease, COPD • Study included patients with a wide variety of conditions in addition to the target population
Soon, 2011[141]	• BNP	Good	• Participants were at widely differing points in natural history of disease • Participants had widely differing degrees of disease severity
Souza, 2007[142]	• BNP • 6MWD (absolute) • Cardiac index • Functional class • RHC-mPAP • RHC-PVR • Right atrial pressure	Good	• None
Taguchi, 2012[143]	• BNP	Good	• None
Takatsuki, 2012[144]	• TRJv • RV size • BNP	Good	• None
Takatsuki, 2012[145]	• BNP	Good	• None
Takatsuki, 2012[146]	• BNP (BNP and NT-proBNP) • 6MWD • RHC-mPAP • RHC-RAP • RHC-PVRi • RHC-CI • TRJv	Good	• None
Takeda, 2010[147]	• BNP • Mortality	Good	• None

Study	Index Tests/Comparators	Quality	Limitations to Applicability
Torbicki, 2003[148]	• FAC • BNP • Pericardial effusion • RA size • Troponin T • Mortality	Good	• None
Utsunomiya, 2011[149]	• BNP • RA size • RIMP/MPI/Tei Index • Mortality	Fair	• None
Utsunomiya, 2009[150]	• RA size • Right atrial pressure • RIMP/MPI/Tei Index	Good	• None
Van Albada, 2008[151]	• Uric acid • Cardiac index • Mortality • RHC-mPAP • RHC-PVR	Good	• Potential adverse events associated with testing or treatment were not measured or reported
Vizza, 2012[152]	• ET-1 • BNP • WHO FC • RHC-mPAP • RHC-CI • RHC-PVR • Clinical worsening	Good	• None
Vizza, 2008[153]	• Endothelin-1 • BNP	Good	• None
Voelkel, 2000[154]	• Uric acid • RHC-mPAP • Right atrial pressure	Good	• None
Williams, 2006[61]	• BNP • 10-fold increase from baseline levels	Fair	• None
Wilkins, 2005[155]	• RV size • Cardiac index • RIMP/MPI/Tei Index • RA size • BNP	Good	• None
Yamada, 2012[156]	• BNP • Uric acid • Mortality • Hospitalization	Good	• None

Study	Index Tests/Comparators	Quality	Limitations to Applicability
Yanagisawa, 2012[157]	• BNP	Good	• None
Yang, 2012[158]	• RV size • mPAP	Fair	• None
Yoshida, 2012[159]	• BNP • mPAP	Fair	• None
Zafrir, 2007[160]	• RA size • RIMP/MPI/Tei Index • RVEF	Good	• None
Zeng, 2011[161]	• BNP	Good	• None
Zhao, 2012[162]	• Uric acid • Mortality	Good	• None

Abbreviations: 6MWD=6-minute walk distance; BNP=brain natriuretic peptide; CHF=congestive heart failure; CTEPH=chronic thromboembolic pulmonary hypertension; CVD=collagen vascular disease; DLCO=diffusion capacity of the lung for carbon monoxide; FAC=fractional area change; mPAP=mean pulmonary artery pressure; MPI=myocardial performance index; NT-proBNP=N-terminal pro-B-type natriuretic peptide; NYHA=New York Heart Association; PAH=pulmonary arterial hypertension; PH=pulmonary hypertension; PPH=primary pulmonary hypertension; PVR=pulmonary vascular resistance; RA=right atrium; RHC=right heart catheterization; RIMP=right index of myocardial performance; RV=right ventricle; RVEF=right ventricular ejection fraction; S'=tricuspid lateral annular systolic velocity; sPAP=systolic pulmonary artery pressure; SSc=systemic sclerosis; TAPSE=tricuspid annular plane systolic excursion; TDI=tissue Doppler imaging; TRV=tricuspid regurgitant jet velocity; VSD=ventricular septal defect; VTI_{RVOT}=velocity-time integral of right ventricular outflow tract

Table D-3. Quality and applicability for KQ 3 studies

Study	Intervention/Comparator	Quality	Limitations to Applicability
Badesch, 2000[163]	• Epoprostenol ≤2 ng/kg, then adjusted • Conventional therapy only	Fair	• None
Barst, 1996[65] Primary Pulmonary Hypertension Study	• Epoprostenol ≤4 ng/kg, then adjusted • Conventional therapy only	Good	• None
Barst, 2010[164] ASSET-1	• Bosentan 62.5 mg BID, then 125 mg BID • Placebo	Fair	• None
Barst, 2010[164] ASSET-2	• Bosentan 62.5 mg BID, then 125 mg BID • Placebo	Fair	• None
Barst, 2011[165] STARTS-1	• Low dose sildenafil • Medium dose sildenafil • High dose sildenafil • Placebo	Fair	• None
Bharani, 2007[69]	• Tadalafil 20 mg daily • Placebo 20 mg daily	Fair	• Intervention (active arm) was not similar to that used in routine clinical practice

Study	Intervention/Comparator	Quality	Limitations to Applicability
Channick, 2001[75] Badesch, 2002[76]	• Bosentan 62.5 mg BID, then 125 mg BID • Placebo	Good	• Potential adverse events associated with testing or treatment were not measured or reported
Fix, 2007[166]	• Epoprostenol 1 ng/kg/min, then titrated to mean dose of 29 ng/kg/min • Non-epoprostenol group	Fair	• None
Galie, 2005[167] Badesch, 2007[168] Rubin, 2011[169] SUPER	• Sildenafil 20 mg TID • Sildenafil 40 mg TID • Sildenafil 80 mg TID • Placebo	Good	• None
Galie, 2006[170] BREATHE-5	• Bosentan 62.5 mg BID, then 125 mg BID • Placebo	Good	• None
Galie, 2008[171] EARLY	• Bosentan 62.5 mg BID, then 125 mg BID • Placebo	Good	• None
Galie, 2008[88] Shapiro, 2012[90] ARIES-1	• Ambrisentan 5 mg daily • Ambrisentan 10 mg daily • Placebo	Good	• None
Galie, 2008[88] Shapiro, 2012[90] ARIES-2	• Ambrisentan 2.5 mg daily • Ambrisentan 5 mg daily • Placebo	Good	• None
Galie, 2009[172] Barst, 2011[173] Oudiz, 2012[174] PHIRST	• Tadalafil 2.5 mg daily • Tadalafil 10 mg daily • Tadalafil 20 mg daily • Tadalafil 40 mg daily • Placebo	Good	• None
Higenbottam, 1993[175]	• Epoprostenol, initial mean dose 5.2 (0.5) ng/kg/min then titrated up to mean 18.7 (4.5) ng/kg/min • No epoprostenol	Fair	• Study population was inadequately described to assess the applicability of this study • Study selectively recruited participants who demonstrated a history of favorable or unfavorable response to the drug/intervention of interest • Included patients did not match the review question • Potential adverse events associated with testing or treatment were not measured or reported

Study	Intervention/Comparator	Quality	Limitations to Applicability
Hiremath, 2010[176] TRUST	• Treprostinil 4 ng/kg/min, then adjusted • Placebo	Fair	• Study population was inadequately described to assess the applicability of this study • Cointerventions/treatments did not adequately reflect routine clinical practice • Care delivery setting was widely divergent from the current typical US setting
Hoeper, 2006[177] COMBI	• Bosentan 125 mg BID + iloprost (aerosolized) • Bosentan 125 mg	Fair	• None
Hoeper, 2007[178]	• Bosentan 62.5 mg BID x 4 weeks, then 125 mg thereafter • Iloprost (aerosolized) 5 mcg 6x daily	Fair	• None
Humbert, 2004[179] BREATHE-2	• Epoprostenol + bosentan 62.5 mg BID, then 125 mg BID • Epoprostenol + placebo	Good	• None
Jacobs, 2009[106]	• Epoprostenol titrated to 6-8 ng/kg/min after 1 week (N=6) • Treprostinil gradually increased to 10 ng/kg/min after 1 week, then 20 ng/kg/min after 6 weeks (N=10)	Fair	• None
Jing, 2011[180] EVALUATION	• Vardenafil 5 mg qD, then 5 mg BID • Placebo	Good	• None
Kemp, 2012[181]	• Epoprostenol/bosentan combined • Epoprostenol monotherapy	Fair	• None
McLaughlin, 2003[182]	• Treprostinil 2.5-5.0 ng/kg/min, then adjusted • Placebo	Poor	• None
McLaughlin, 2006[183]	• Bosentan + iloprost (aerosolized) • Bosentan + placebo	Good	• None
McLaughlin, 2010[119] Frantz, 2012[120] TRIUMPH 1	• Treprostinil (aerosolized) • Placebo	Good	• None
Mukhopadhyay, 2011[184]	• Tadalafil 40 mg daily • Placebo	Fair	• Care delivery setting was widely divergent from the current typical US setting
Olschewski, 2002[185]	• Iloprost (aerosolized) • Placebo	Good	• None
Olschewski, 2010[186] AIR	• Iloprost (aerosolized) • Standard therapy only	Fair	• None

Study	Intervention/Comparator	Quality	Limitations to Applicability
Reichenberger, 2011[187]	• Epoprostenol • Iloprost up to 20 mcg per breath, max 120 mcg total daily dose	Fair	• None
Rich, 2012[188]	• IV treprostinil in epoprostenol diluent • IV epoprostenol in epoprostenol diluent • IV treprostinil in native diluent	Fair	• Participants had widely differing degrees of disease severity • Study selectively recruited participants who demonstrated a history of favorable or unfavorable response to the drug/intervention of interest
Rubin, 2002[189] Galie, 2003[190] Denton, 2006[191] BREATHE	• Bosentan 62.5 mg BID, then 125 mg BID • Bosentan 62.5 mg BID, then 250 mg BID • Placebo	Good	• None
Rubin, 1990[192] Barst, 1994[193]	• Intravenous epoprostenol 1–2 ng/kg per minute initially, then increased as tolerated • Conventional therapy	Good	• Study selectively recruited participants who demonstrated a history of favorable or unfavorable response to the drug/intervention of interest • Current methods for treatment of the disease have changed since the study took place
Sastry, 2007[194]	• Sildenafil 25-50 mg TID • Conventional therapy	Fair	• None
Simonneau, 2002[195] Treprostinil Study	• Treprostinil 1.25 ng/kg/min, then adjusted • Placebo	Good	• None
Simonneau, 2008[196] PACES	• Sildenafil 20 mg TID, then up to 80 mg TID • Placebo	Good	• None
Wilkins, 2005[155] SERAPH	• Bosentan 62.5 mg BID, then 125 mg BID • Sildenafil 50 mg BID, then 50 mg TID	Good	• None
Zeng, 2011[197]	• Sildenafil • Conventional therapy	Fair	• None

Abbreviations: BID=twice daily; kg=kilogram; mcg=microgram; mg=milligram; ng=nanogram; TID=three times daily

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Appendix E. List of Excluded Studies

All studies listed below were reviewed in their full-text version and excluded for the reason shown in italics. Reasons for exclusion signify only the usefulness of the articles for this study and are not intended as criticisms of the articles.

Abbas AE, Fortuin FD, Schiller NB, et al. Echocardiographic determination of mean pulmonary artery pressure. Am J Cardiol. 2003;92(11):1373-6. PMID: 14636929. *Exclude - No comparisons of interest*

Abdelwahed A, Klada E, Vaghasia P, et al. Cardiac-MRI derived index to diagnose pulmonary Hypertension. Chest. 2011;140(4). *Exclude - Not a full publication*

Abdul-Salam VB, Paul GA, Ali JO, et al. Identification of plasma protein biomarkers associated with idiopathic pulmonary arterial hypertension. Proteomics. 2006;6(7):2286-94. PMID: 16493708. *Exclude - No comparisons of interest*

Abman SH. Pulmonary hypertension in older children: new approaches and therapies. Paediatr Respir Rev. 2006;7 Suppl 1:S177-9. PMID: 16798555. *Exclude - Background Other*

Acikel M, Yilmaz M, Gurlertop Y, et al. Evaluation of left ventricular diastolic function by doppler echocardiography and tissue doppler imaging in chronic cor pulmonale. Turk Kardiyoloji Dernegi Arsivi. 2003;31(7):384-391. *Exclude - not available in English*.

Acosta Colman MI, Avila Pedretti G, Acosta ME, et al. Can we predict the severity of pulmonary hypertension in patients with scleroderma? Reumatologia Clinica. 2012. *Exclude - Not a full publication*

Adatia I, Beghetti M. Early postoperative care of patients with pulmonary hypertension associated with congenital cardiac disease. Cardiol Young. 2009;19(4):315-9. PMID: 19493364. *Exclude - Not a full publication*

Adnot S, Raffestin B, Eddahibi S. Nitric oxide in the pulmonary circulation. Monaldi Arch Chest Dis. 1996;51(6):519-27. PMID: 9046167. *Exclude - Does not include intervention of interest*

Adriaenssens T, Delcroix M, Van Deyk K, et al. Advanced therapy may delay the need for transplantation in patients with the Eisenmenger syndrome. Eur Heart J. 2006;27(12):1472-7. PMID: 16707548. *Exclude - No comparisons of interest*

Aduen JF, Castello R, Daniels JT, et al. Accuracy and precision of three echocardiographic methods for estimating mean pulmonary artery pressure. Chest. 2011;139(2):347-52. PMID: 20651021. *Exclude - Does not include intervention of interest*

Aessopos A, Farmakis D, Deftereos S, et al. Cardiovascular effects of splenomegaly and splenectomy in beta-thalassemia. Ann Hematol. 2005;84(6):353-7. PMID: 15711802. *Exclude - Does not include intervention of interest*

Aessopos A, Farmakis D, Deftereos S, et al. Thalassemia heart disease: a comparative evaluation of thalassemia major and thalassemia intermedia. Chest. 2005;127(5):1523-30. PMID: 15888823. *Exclude - Does not include intervention of interest*

Aessopos A, Farmakis D, Hatziliami A, et al. Cardiac status in well-treated patients with thalassemia major. Eur J Haematol. 2004;73(5):359-66. PMID: 15458515. *Exclude - Does not include intervention of interest*

Aessopos A, Farmakis D, Karagiorga M, et al. Cardiac involvement in thalassemia intermedia: a multicenter study. Blood. 2001;97(11):3411-6. PMID: 11369631. *Exclude - Does not include intervention of interest*

Aessopos A, Stamatelos G, Skoumas V, et al. Pulmonary hypertension and right heart failure in patients with beta-thalassemia intermedia. Chest. 1995;107(1):50-3. PMID: 7813310. *Exclude - Does not include intervention of interest*

Afifi S, Shayan S, Al-Qamari A. Pulmonary hypertension and right ventricular function: interdependence in pathophysiology and management. Int Anesthesiol Clin. 2009;47(1):97-120. PMID: 19131755. *Exclude - Not a full publication*

Agapito AF, Sousa L, Oliveira JA, et al. Eisenmenger syndrome in the adult--experience with new drugs for the treatment of pulmonary hypertension. Rev Port Cardiol. 2005;24(3):421-31. PMID: 15929625. *Exclude - No comparisons of interest*

Aggarwal P, Patial RK, Negi PC, et al. Oral tadalafil in pulmonary artery hypertension: a prospective study. Indian Heart J. 2007;59(4):329-35. PMID: 19126938. *Exclude - No study population of interest*

Aggarwal SK, Mishra J, Sai V, et al. Aortopulmonary window in adults: diagnosis and treatment of late-presenting patients. Congenit Heart Dis. 2008;3(5):341-6. PMID: 18837813. *Exclude - Does not include intervention of interest*

Aguilar RV, Farber HW. Epoprostenol (prostacyclin) therapy in HIV-associated pulmonary hypertension. Am J Respir Crit Care Med. 2000;162(5):1846-50. PMID: 11069824. *Exclude - No comparisons of interest*

Ahearn GS, Tapson VF, Rebeiz A, et al. Electrocardiography to define clinical status in primary pulmonary hypertension and pulmonary arterial hypertension secondary to collagen vascular disease. Chest. 2002;122(2):524-7. PMID: 12171826. *Exclude - No comparisons of interest*

Ahmadi-Simab K, Hellmich B, Gross WL. Bosentan for severe pulmonary arterial hypertension related to systemic sclerosis with interstitial lung disease. Eur J Clin Invest. 2006;36 Suppl 3:44-8. PMID: 16919010. *Exclude - No comparisons of interest*

Ahmed AE, Ibrahim AS, Elshafie SM. Pulmonary hypertension in patients with treated pulmonary tuberculosis: analysis of 14 consecutive cases. Clin Med Insights Circ Respir Pulm Med. 2011;5:1-5. PMID: 21339885. *Exclude - No study population of interest*

Ahmed AM, El-Shamaa MF. Asymptomatic cardiac involvement in children with Systemic Lupus Erythematosus. J Med Sci (Pakistan). 2006;6(6):944-949. *Exclude - no primary or secondary outcomes of interest*

Ahmed S, Siddiqui AK, Sadiq A, et al. Echocardiographic abnormalities in sickle cell disease. Am J Hematol. 2004;76(3):195-8. PMID: 15224351. *Exclude - Does not include intervention of interest*

Airo P, Rossi M, Scarsi M, et al. Disease-modifying effects of long-term cyclic iloprost therapy in systemic sclerosis. A retrospective analysis and comparison with a control group. Clin Exp Rheumatol. 2007;25(5):722-7. PMID: 18078620. *Exclude - No comparisons of interest*

Ajami GH, Borzoee M, Radvar M, et al. Comparison of the effectiveness of oral sildenafil versus oxygen administration as a test for feasibility of operation for patients with secondary pulmonary arterial hypertension. Pediatr Cardiol. 2008;29(3):552-5. PMID: 18058160. *Exclude - No comparisons of interest*

Akagi S, Matsubara H, Miyaji K, et al. Additional effects of bosentan in patients with idiopathic pulmonary arterial hypertension already treated with high-dose epoprostenol. Circ J. 2008;72(7):1142-6. PMID: 18577825. *Exclude - No comparisons of interest*

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Appendix F. Study Characteristics Tables (KQ 1 and KQ 2)

Note: The study characteristics table for KQ 3 is in the main report.

Table F-1. Study characteristics table for KQ 1

Study	Population Total N	Test Measures	Study Objectives	Quality
Ajami, 2011[1]	Children and young adults with congenital heart disease referred for RHC N=20	TRV/VTI_{RVOT}	Accuracy of TRV/VTI_{RVOT} for diagnosing elevated PVR	Good
Allanore, 2008[2]	SSc patients with echocardiography sPAP<40 mmHg and no NYHA III/IV symptoms N=101	NT-proBNP, plasma sPAP	Screening for prospective development of PAH (predicting development of PAH in at-risk population)	Good
Arcasoy 2003[3]	Patients with advanced lung disease undergoing evaluation for lung transplantation N=374	sPAP RAP	Estimate performance characteristics of echocardiography compared with RHC in determining sPAP and diagnosing PH	Good
Bogdan, 1998[4]	PAH patients and controls N=19	cGMP, urine	Test association of PAH with urine cGMP	Poor
Bonderman, 2011[5]	Referred for evaluation of suspected PAH; more than half had NYHA III/IV symptoms N=372	NT-proBNP sPAP RA size RV size TAPSE	Diagnostic accuracy for distinguishing PAH from secondary PH Precision/calibration of echocardiographic measures	Good
Cavagna, 2010[6]	SSc patients; symptoms not described N=135	BNP NT-proBNP	Screening for PAH Discrimination between PAH or not Reference standard based on echocardiography sPAP screening with RHC verification of positives	Good
Cevik, 2012[7]	Children with pulmonary hypertension, with and without congenital heart disease N=70	RIMP/MPI/Tei index mPAP S' TAPSE TRV/VTI_{RVOT}	Evaluation of RV function using transthoracic echocardiography	Fair
Ciurzynski, 2011[8]	SSc patients. Patients with signs or symptoms of heart or lung disease excluded N=71	Transtricuspid gradient rest/exercise	Association with diagnosis of PAH	Good
Colle, 2003[9]	Liver transplant candidates N=165	sPAP	Screening for portopulmonary hypertension	Good

Study	Population Total N	Test Measures	Study Objectives	Quality
Condliffe, 2011[10]	SSc patients with suspected PAH; symptoms not described N=89	Tricuspid gradient	Discrimination between PAH or not Reference standard=RHC	Fair
Dahiya, 2010[11]	Referred for evaluation of suspected PH; all patients had dyspnea N=114	TRV/VTI_{RVOT}	Diagnostic accuracy, calibration, and precision of echocardiography estimation of elevated PVR	Good
Denton, 1997[12]	SSc patients suspected of PAH, most due to reduced DLCO N=93	RV size sPAP	Diagnostic accuracy, discrimination of echocardiography for diagnosing PAH	Fair
Farber, 2011[13]	Patients with PAH N=1883	sPAP RAP	Accuracy of echocardiography for sPAP and RAP	Fair
Fisher, 2009[14]	Patients undergoing RHC for known or suspected PAH; symptoms not described N=65	sPAP Transtricuspid gradient	Precision/calibration of echocardiography for mPAP, sPAP compared with RHC	Good
Fitzgerald, 2012[15]	Sickle cell disease with TRV ≥2.5 m/s and RHC N=75	TRV mPAP	Comparison of TRV measurement to RHC for diagnosing PH	Poor
Fonseca, 2012[16]	Sickle cell disease; symptoms not described N=80	TRV Uric acid	Screening for PAH Echocardiography screening of TRV with RHC verification of positives	Fair
Frea, 2011[17]	SSc patients with no signs or symptoms of PAH N=76	NT-proBNP FAC RIMP/MPI/Tei index RV size TRV/VTI_{RVOT} TAPSE	Screening for prospective development of PAH (Predicting development of PAH in at-risk population)	Fair
Fukuda, 2011[18]	Patients with known PH N=67	FAC TAPSE RIMP/MPI/Tei index sPAP	Correlation between echocardiography and RHC hemodynamics in patient with elevated mPAP	Fair
Ghio, 2004[19]	HIV and confirmed PAH. Controls with HIV and no known cardiac or pulmonary disease N=93	NT-proBNP	Diagnostic accuracy for NT-proBNP for discriminating HIV-positive PAH patients from HIV-positive controls	Fair
Gialafos, 2008[20]	SSc patients. Some were symptomatic N=106	NT-proBNP RIMP/MPI/Tei index	Association with diagnosis of PAH	Fair
Hachulla, 2005[21]	SSc patients; some symptomatic N=599	TRV	Screening for PAH in at-risk population	Poor
Hammerstingl, 2012[22]	Patients with PH undergoing RHC and transthoracic echocardiography N=155	sPAP mPAP	Diagnosis of PH and differentiating between pre- and postcapillary PH	Fair
Hsu, 2008[23]	SSc patients with dyspnea or other clinical features suggestive of PAH N=49	sPAP	Diagnostic accuracy for diagnosing PAH	Good

Study	Population Total N	Test Measures	Study Objectives	Quality
Hua, 2009[24]	Liver transplant candidates N=105	sPAP	Diagnostic accuracy for portopulmonary hypertension	Good
Jansa, 2012[25]	SSc patients some with dyspnea N=203	TRV	Screening for PAH in at-risk population	Fair
Kovacs, 2010[26]	Patients with CVD some with symptoms N=52	sPAP rest and exercise	Screening for PAH in at-risk population	Good
Lindqvist, 2011[27]	Patients with PH undergoing RHC N=30	TRV/VTI_{RVOT}	Accuracy for diagnosis of elevated PVR Precision/calibration of echocardiography estimate of PVR	Fair
Low, 2011[28]	Referred for evaluation of suspected or definite PAH, most with symptoms N=200	Transtricuspid gradient	Diagnostic accuracy for diagnosing PAH	Poor
Machado, 2006[29]	Sickle cell disease N=416	NT-proBNP	Association between biomarker and hemodynamic measures. Diagnosis based on echocardiography screen with partial verification by RHC of some test positives.	Poor
McLean, 2007[30]	Referred for echocardiography with adequate TR jet on Doppler, nearly all with symptoms N=108	RV end-diastolic diameter (RVD) time to peak (RV tricuspid annular motion by TDI, time from beginning of IC to first systolic myocardial peak)	Correlation between echocardiography RVD/time to peak and RHC PASP	Poor
Mourani, 2008[31]	Children under 2 years of age undergoing RHC for chronic lung disease N=25	RA size RV size Transtricuspid gradient	Asses echocardiography feasibility, calibration for estimating hemodynamics, and accuracy for diagnosis of PAH	Fair
Mukerjee, 2004[32]	SSc patients with suspected PAH, symptoms of exercise limitation and reduced DLCO N=137	sPAP	Accuracy of echocardiography sPAP at different thresholds for diagnosis of PAH	Fair
Murata, 1997[33]	SSc patients. Symptoms not described, but most had reduced DLCO N=135	sPAP	Precision/calibration of echocardiography for estimating invasive pulmonary hemodynamics	Fair
Nakayama, 1998[34]	Patients with known, symptomatic CTEPH or PPH N=35	sPAP mPAP	Accuracy of echocardiography for discrimination between CTEPH and PPH	Fair
Nogami, 2009[35]	Suspected pulmonary hypertension; all patients symptomatic N=29	sPAP	Precision/calibration of echocardiography for estimating invasive pulmonary hemodynamics	Good

Study	Population Total N	Test Measures	Study Objectives	Quality
Phung, 2009[36]	SSc patient referred with or without suspicion of PAH; 10% had NYHA III/IV symptoms N=184	sPAP	Accuracy of echocardiography sPAP for diagnosing PAH	Good
Pilatis, 2000[37]	Liver transplant candidates N=55	RV size sPAP	Accuracy of echocardiography for diagnosing portopulmonary hypertension	Fair
Rajagopalan, 2008[38] Rajagopalan, 2007[39]	Known pulmonary hypertension N=52	TRV/VTI_{RVOT} sPAP S'	Accuracy of echocardiography for estimating PVR in PH patients Calibration/precision of echocardiography for estimating RHC hemodynamics	Fair
Rajaram, 2012[40]	Connective tissue disease patients with suspected PH N=81	sPAP mPAP Pericardial effusion	Comparison of magnetic resonance imaging, computed tomography, and echocardiography for diagnosing PAH	Fair
Rich, 2011[41]	Patients with both RHC and Doppler echo N=183	sPAP	Calibration/precision of echocardiography for estimating RHC hemodynamics	Good
Roeleveld, 2005[42]	Known PH N=47	sPAP	Calibration/precision of echocardiography for estimating RHC hemodynamics	Fair
Roule, 2010[43]	Known PH N=37	TRV TRV/VTI_{RVOT}	Calibration/precision for estimating RHC hemodynamics at elevated PA pressures Accuracy for diagnosing elevated PVR in PH patients	Good
Ruan, 2007[44]	Known PAH and healthy controls N=180	FAC RV size sPAP	Diagnostic accuracy of echocardiography for discriminating PAH and control patients	Fair
Ruiz-Irastorza, 2012[45]	Systemic lupus erythematosus patients with or without suspicion of PAH N=245	sPAP mPAP	Prevalence of and strategy for diagnosing PH in patients with lupus	Fair
Sanli, 2012[46]	Congenital heart disease with and without known PAH N=70	RV size mPAP Nitric oxide RIMP/MPI/Tei index TAPSE	Relationship between biomarkers and hemodynamic measurements	Fair
Selby, 2012[47]	Patients with HIV infection with or without suspicion of PAH N=129	sPAP	Comparison of sPAP measured by echocardiography versus RHC	Fair
Selimovic, 2007[48]	Patients with suspected pulmonary vascular disease. 37/42 NYHA III/IV N=42	sPAP mPAP	Calibration/precision of echocardiography for estimating RHC hemodynamics	Good
Simeoni, 2008[49]	Known SSc-associated PAH and controls with SSc but no PAH N=20	NT-proBNP	Diagnostic accuracy of NT-proBNP for discriminating PAH and control patients	Poor

Study	Population Total N	Test Measures	Study Objectives	Quality
Steen, 2008[50]	SSc patients with suspected PAH based on symptoms or signs N=54	sPAP rest/exercise	Accuracy of rest/exercise echocardiography to diagnose PAH	Fair
Takatsuki, 2012[51]	Children with idiopathic PAH N=102	S' mPAP	Assessing disease severity and prognostic value with tissue Doppler imaging	Fair
Tei, 1996[52]	Known PPH and health controls N=53	RIMP/MPI/Tei index	Association of Tei index with PPH versus normal controls	Poor
Thakkar, 2012[53]	SSc patients with known PAH, high risk for PAH, interstitial lung disease, or no cardiopulmonary disease N=94	sPAP NT-proBNP	NT-proBNP as a replacement for transthoracic echocardiography in screening for SSc-related PAH	Fair
Tian, 2011[54]	Suspected PH based on symptoms N=42	sPAP mPAP	Calibration/precision of echocardiography for estimating RHC hemodynamics	Fair
Torregrosa, 2001[55]	Liver transplant candidates N=94	sPAP	Accuracy for diagnosing portopulmonary hypertension	Fair
Toyono, 2008[56]	Children with VSD and severe PH N=24	BNP	Correlation between BNP levels and invasive PVR	Good
Tutar, 1999[57]	Children with left-to-right shunt and health controls N=23	Endothelin-1, plasma	Association of endothelin-1 levels and pulmonary hypertension	Fair
Vlahos, 2007[58]	Known or suspected pulmonary hypertension N=12	TRV/VTI_{RVOT}	Accuracy of echocardiography for diagnosing elevated PVR	Poor
Vonk, 2007[59]	Connective tissue diseases. One-third NYHA III/IV N=98	RIMP/MPI/Tei index sPAP	Accuracy for diagnosis of PAH or not	Fair
Willens, 2008[60]	Patients with known PH and elevated sPAP and controls with CHF and elevated sPAP N=47	sPAP	Association of sPAP with PH versus CHF	Fair
Williams, 2006[61]	SSc patients with PAH and controls with SSc but without PAH N=109	NT-proBNP	Accuracy for diagnosis of PAH	Fair

Abbreviations: BNP=brain natriuretic peptide; CHF=congestive heart failure; CTEPH=chronic thromboembolic pulmonary hypertension; CVD=collagen vascular disease; DLCO=diffusion capacity of the lung for carbon monoxide; FAC=fractional area change; mPAP=mean pulmonary artery pressure; MPI=myocardial performance index; NT-proBNP=N-terminal pro-B-type natriuretic peptide; NYHA=New York Heart Association; PAH=pulmonary arterial hypertension; PH=pulmonary hypertension; PPH=primary pulmonary hypertension; PVR=pulmonary vascular resistance; RA=right atrium; RHC=right heart catheterization; RIMP=right index of myocardial performance; RV=right ventricle; S'=tricuspid lateral annular systolic velocity; sPAP=systolic pulmonary artery pressure; SSc=systemic sclerosis; TAPSE=tricuspid annular plane systolic excursion; TDI=tissue Doppler imaging; TRV=tricuspid regurgitant jet velocity; VSD=ventricular septal defect; VTI_{RVOT}=velocity-time integral of right ventricular outflow tract

Table F-2. Study characteristics table for KQ 2

Andreassen, 2006[62] Europe	Adults with suspected chronic precapillary PH N=61 42:19	BNP BNP	Cardiac index Functional class RHC-mPAP RHC-PVR RHC-sPAP RAP Mortality	Correlation Odds ratio	Good
Badesch, 2012[63] Badesch 2011[64] US/Canada	Adults with PAH N=224 156:68	BNP		Mean change from baseline in response to treatment (ambrisentan)	Good
Barst, 1996[65] US/Canada	Adults with PPH N=81 59:22	mPAP		Change in mean from baseline in response to therapy (epoprostenol)	Good
Bendayan, 2002[66] Asia	Adults and children with PAH N=29 25:4	Uric acid	6MWD (absolute) Functional class Mortality RHC-CO RHC-mPAP	Correlation	Good
Benza, 2010[67] US	Adults with PAH N=2716 NR	BNP >180 BNP <50 Pericardial effusion	Mortality	HR	Good
Bernus, 2009[68] US	Children with PAH N=78 42:26	BNP	Cardiac index Peak TRV PCWP RHC-mPAP RHC-PVR Right atrial pressure RV size TRV	Correlation	Good
Bharani, 2007[69] Asia	Adults and children with suspected or symptomatic PAH N=8 4:4	sPAP		Change in mean in response to therapy (tadalafil)	Fair

Borges, 2006[70] Europe	Chronic PAH N=37 24:13	RIMP/MPI/Tei index TAPSE TAPSE RV size	6MWD (absolute) RHC-PVR	Correlation Change in mean in response to therapy (bosentan ± beraprost or iloprost)	Good
Brierre, 2010[71] Europe	Adults with PAH N=79 36:43	mPAP mPAP ≥ 49 Pericardial effusion RIMP/MPI/Tei index RIMP/MPI/Tei index ≥0.98 TAPSE	Mortality	HR	Good
Bustamante-Labarta, 2002[72] South America	Adults with PPH N=25 19:6	RA size	Survival free from lung transplant	HR	Good
Campana, 2004[73] Europe	Adults with pre-capillary PH N=22 14:8	BNP Cardiac index FAC BNP RV size TAPSE	mPAP Right atrial pressure RVEF TAPSE	Correlation Changes in means in response to therapy (epoprostenol)	Good
Cella, 2009[74] Europe	Adults with PAH associated with CTD N=18 13:5	RVSP Nitric oxide	6MWD (change)	Correlation Change in mean over time in response to therapy (bosentan)	Good
Channick, 2001[75] Badesch 2002[76] US/Europe	Adults with PPH or PAH associated with scleroderma N=32 28:4	mPAP		Change in mean from baseline in response to therapy (bosentan)	Good

Chin, 2007[77] US	Epoprostenol-treated patients with pulmonary hypertension N=27 19:8	BNP	6MWD (absolute) PCWP RHC-CO RHC-mPAP RHC-PVR Right atrial pressure	Correlation	Good
Dimitroulas, 2007[78] Europe	Adults with PAH associated with scleroderma N=10 9:1	BNP		Change in median over time in response to therapy (Bosentan)	Good
D'Alto, 2010[79] Europe	Adults with PAH due to CHD N=32 18:14	BNP		Change in mean in response to therapy (bosentan + sildenafil)	Fair
Dyer, 2006[80] US	Children with IPAH N=12 NR	RIMP/MPI/Tei index	RHC-mPAP	Correlation	Fair
Elstein, 2004[81] Asia	Adults and children with Gaucher disease N=47 27:20	BNP	Tricuspid insufficiency	Correlation with stratified TI values	Good
Fahmy Elnoamany, 2007[82] Africa	Adults with arterial PH with different cardiac pathologies N=53 8:45	Endothelin-1 sPAP	RHC-sPAP RIMP/MPI/Tei Index RVEF sPAP RHC-sPAP	Correlation	Fair
Feliciano, 2005[83] Europe	Adults with severe PAH N=11 9:2	RIMP/MPI/Tei index		Change in mean in response to therapy (bosentan or Iloprost)	Good

Fijalkowska, 2006[84] Europe	Adults with PH N=55 43:12	BNP FAC BNP BNP Pericardial effusion RA size RIMP/MPI/Tei index RV size Troponin T	6MWD (absolute) Cardiac index Functional class Peak TRV Pericardial effusion RHC-mPAP RHC-PVR Right atrial pressure RIMP/MPI/Tei Index RV size Troponin Mortality	Correlation HR	Good
Filusch, 2010[85] Europe	Adults with PAH N=55 33:22	cTroponin T hsTroponin T BNP	Mortality WHO class	Sensitivity Specificity NPV PPV	Good
Forfia, 2006[86] US	Adults with PH N=63 52:11	TAPSE TAPSE	RHC-PVR Mortality	Correlation HR	Good
Friedberg, 2006[87] US	Adults and children who had undergone RHC N=112 48:64	mPAP BNP sPAP	RHC-mPAP RHC-sPAP	Correlation	Good
Galie, 2008[88] Oudiz 2009[89] Shapiro 2012[90] US/Europe/Mexico/ South America/ Australia/NZ	Adults with PAH N=201 168:33	BNP		Change in mean in response to therapy (ambrisentan)	Good

Gan, 2006[91] Europe	Adults with PH N=30 22:8	BNP	6MWD (absolute) Cardiac index RHC-mPAP RHC-PVR Right atrial pressure RVEF	Correlation	Good
Ghio, 2010[92] Europe	Adults with IPAH N=59 37:22	FAC Pericardial effusion RIMP/MPI/Tei index sPAP TAPSE	Mortality	HR	Good
Ghofrani, 2002[93] Europe	Adults with severe precapillary PH. N=20 (36 tests) NR	BNP cGMP	RHC-PVR Cyclic guanosine monophosphate RHC-PVR	Correlation	Fair
Goto, 2010[94] Asia	Adults with PAH N=46 34:12	BNP sPAP	RHC-mPAP RHC-sPAP	Correlation	Good
Grapsa, 2007[95] UK	Adults with PH N=93 50:43	RIMP/MPI/Tei index	Pericardial effusion RA size TRV	Correlation	Good
Grubstein, 2008[96] Asia	Adults with PH N=38 27:11	sPAP	RHC-sPAP	Correlation	Fair
Haddad, 2009[97] US	Adults with PAH N=51 35:16	mPAP sPAP	RHC-mPAP RHC-sPAP	Correlation	Good
Halank, 2011[98] Europe	Adults with portopulmonary hypertension N=14 9:5	BNP	Median	Change in median over time in response to therapy (ambrisentan)	Fair
Hampole, 2009[99] US	Adults with PH N=162 126:36	BNP	Mortality	HR	Good
Heresi, 2012[100] US	Adults with PAH N=68 62:6	cTnI (detectable vs. nondetectable)	BNP NYHA class RA size 6MWD	Correlation	Good

Heresi, 2010[101] US	Adults with PPH N=40 37:3	BNP	6MWD (absolute) Cardiac index RHC-mPAP RHC-PVR Right atrial pressure Mortality	Correlation HR	Good
Hinderliter, 1997[102] Other	Adults with PPH N=81 59:22	FAC Pericardial effusion RV size sPAP RV size FAC TRV	6MWD (absolute) Cardiac index RHC-mPAP Right atrial pressure 6MWD (absolute) Cardiac index (CI) RHC-mPAP Right atrial pressure 6MWD (absolute) Cardiac index RHC-mPAP Right atrial pressure RHC-sPAP	Correlation Correlation Correlation Correlation Change in mean from baseline in response to therapy (epoprostenol)	Fair
Hiramoto, 2009[103] Asia	Adults with PAH N=16 11:5	BNP	Endothelin-1	Changes in mean stratified by % change in ET-1	Fair
Ho, 2009[104] Asia	Adults with PAH N=6 4:2	RIMP/MPI/Tei Index FAC BNP sPAP RVEF		Changes in median in response to therapy (bosentan)	Good
Homma, 2001[105] US	Adults with PH N=8 5:3	sPAP	RHC-sPAP	Correlation	Good

Jacobs, 2009[106] Europe	Adults with idiopathic PAH N=16 13:3	BNP		Change in mean in response to therapy	Fair
Kaya, 2012[107] NR	Adults and children with Eisenmenger syndrome N=23 13:10	RV size RA size sPAP s-prime		Change in mean over time in response to therapy (bosentan)	Good
Keogh, 2011[108] Australia/NZ	Adults with PAH N=112 89:23	sPAP		Change in mean in response to therapy (monotherapy vs. combination therapy)	Fair
Knirsch, 2011[109] Europe	Children with heart disease N=103 NR	BNP		Changes in mean in response to therapy (standardized protocol)	Good
Kopec, 2012[110] Europe	Adults with Eisenmenger syndrome N=7 4:3	BNP ET-1		Change in median over time in response to therapy (bosentan)	Fair
Lammers, 2009[111] UK	Children with PH N=50 18:32	BNP	6MWD (absolute) Functional class	Correlation	Good
Langleben, 1999[112] US/Canada	Patients with PPH N=18 NR	Endothelin-1		Change in mean in response to therapy	Good
Leuchte, 2005[113] Europe	Adults with PAH N=30 18:12	Change in BNP BNP	6MWD (absolute) Cardiac index RHC-CO RHC-mPAP RHC-PVR Right atrial pressure	Correlation Changes in mean levels over time (no specific therapy)	Good
Lorenzen, 2011[114] Europe	Adults with PAH N=70 48:22	BNP Uric acid	Mortality	HR	Good

Machado, 2006[29] US	Patients with sickle cell disease N=230 138:92	BNP BNP ≥160, unadjusted ≥160, adjusted log10, adjusted log10, unadjusted	6MWD (absolute) mPAP PCWP RA size RHC-CO RHC-dPAP RHC-PVR RHC-sPAP RV size TRV Mortality	Correlation HR	Poor
Machado, 2004[115] US	Patients with PAH N=17 17:0	Nitric oxide sPAP	mPAP RHC-sPAP	Correlation	Fair
Mahapatra, 2006[116] US	Adults with PH N=54 41:13	RIMP/MPI/Tei Index RVSP	Mortality	HR	Fair
Mathai, 2011[117] US	Adults with known or suspected PAH N=50 49:1	FAC Peak TRV Pericardial effusion RA size TAPSE	Mortality	HR	Fair
Mauritz, 2011[118] Europe	Adults with PAH N=198 149:49	BNP		Baseline means only	Good
McLaughlin, 2010[119] Frantz, 2012[120] US/Europe	Adults with PH N=235 191:44	BNP		Median change from baseline in response to treatment (treprostinil)	Good
Michelakis, 2002[121] Canada	Adults with PH N=13 9:4	cGMP		Acute change in mean levels after dose of various vasodilators (iNO, sildenafil, iNO + sildenafil)	Fair

Minniti, 2009[122] US	Adults with SCD and PH N=14 10:4	BNP TRV		Change in mean in response to therapy (ambrisentan)	Poor
Montani, 2007[123] Europe	Adults with PAH N=33 21:12	Endothelin-1	Cardiac index RHC-PVR Right atrial pressure	Correlation	Fair
Morishita, 2009[124] Asia	Adults and children with PAH N=7 6:1	Pericardial effusion RA size RA size BNP	Functional class BNP	Correlation Changes in mean in response to therapy (epoprostenol)	Good
Mukerjee, 2003[125] Europe	Adults with systemic sclerosis N=23 21:2	BNP	RHC-mPAP RHC-PVR	Correlation	Good
Nagaya, 2000[126] Asia	Patients with PPH N=60 42:18	ANP ANP BNP BNP	PCWP RHC-CO RHC-mPAP Right atrial pressure Mortality PCWP RHC-CO RHC-mPAP RHC-mPAP RHC-PVR Right atrial pressure RV size Mortality	Correlation HR Correlation HR	Good
Nakayama, 2007[127] Asia	Children with IPAH N=31 15:16	BNP		Change in mean in response to therapy (epoprostenol)	Fair

Nath, 2005[128] US	Adults with PPH N=20 16:4	Peak TRV RIMP/MPI/Tei Index RV size RIMP/MPI/Tei Index RV size sPAP TRV	Functional class	Correlation Mean changes over time in response to therapy (epoprostenol)	Good
Nickel, 2012[129] NR	Adults with IPAH N=109 85:24	BNP Uric acid	Mortality	HR	Fair
Nickel, 2008[130] Europe	Adults with IPAH N=76 52:24	BNP Uric acid	Composite outcome (death or lung transplantation)	HR	Fair
Njaman, 2007[131] Asia	Adults with PH N=90 77:13	Uric acid	Mortality	HR stratified by uric acid levels	Good
Ogawa, 2012[132] Asia	Adults with pulmonary veno-occlusive or pulmonary capillary hemangiomatosis N=8 4:4	BNP		Change in mean over time in response to therapy (epoprostenol)	Fair
Park, 2004[133] US	Adults with PAH N=20 16:4	sPAP BNP	Clinical event	Mean levels at baseline and over time stratified by patients with event vs patients without event	Fair
Pyxaras, 2011[134] Europe	Adults and children with PAH N=60 36:24	sPAP mPAP	RHC-sPAP RHC-mPAP	Correlation	Good
Raymond, 2002[135] Not reported/Unclear	Adults with PPH N=81 59:22	FAC Peak TRV Pericardial effusion RA size	Mortality Composite outcome (death or transplantation)	HR	Fair

Rhodes, 2011[136] Europe	Adults with IPAH N=139 98:41	BNP	6MWD (absolute) Cardiac index PCWP RHC-PVR Right atrial pressure Mortality	Correlation HR	Good
Sadushi-Kolici, 2012[137] NR	Adults with PH N=111 77:39	Pericardial effusion	Mortality	HR	Fair
Schumann, 2010[138] Europe	Adults with PH N=36 17:19	BNP	sPAP	BNP levels stratified by different levels of disease severity	Good
Sebbag, 2001[139] Canada	Adults and children with PPH N=16 13:3	RIMP/MPI/Tei Index SPAP		Changes in mean in response to therapy (epoprostenol)	Good
Shimony, 2012[140] Canada	Adults with PAH N=154 129:25	Pericardial effusion (prevalent v incident)	Mortality	% patients with outcome	Fair
Simeoni, 2008[49] Europe	Adults with systemic sclerosis and PH N=20 18:2	BNP		Changes in mean in response to therapy (bosentan)	Good
Soon, 2011[141] UK	Adults with PH N=63 42:21	BNP		Determination of most accurate log transformed dichotomous BNP variables to predict events	Good
Souza, 2007[142] Not reported/Unclear	Adults with IPAH N=42 10:32	BNP	6MWD (absolute) Cardiac index Functional class RHC-mPAP RHC-PVR Right atrial pressure	Correlation	Good

Taguchi, 2012[143] Asia	Adults and children with IPAH N=65 51:14	BNP		Change in mean over time in response to combination therapy	Good
Takatsuki, 2012[144] US	Children with PAH N=33 22:11	TRJv RV size BNP		Change in mean over time in response to therapy (tadalafil)	Good
Takatsuki, 2012[145] US	Children with PAH N=38 19:19	BNP		Change in mean over time in response to therapy (transition to or addition of ambrisentan)	Good
Takatsuki, 2012[146] US	Children with PAH N=88 46:42	BNP (BNP and NT-proBNP)	6MWD RHC-mPAP RHC-RAP RHC-PVR RHC-CI TRJv	Correlation	Good
Takeda, 2010[147] Asia	Adults with PAH N=37 29:8	BNP	Mortality	HR	Good
Torbicki, 2003[148] Europe	Adults with PAH N=56 43:13	FAC BNP Pericardial effusion RA size Troponin T	Mortality	HR	Good
Utsunomiya, 2011[149] Asia	Adults with PH N=50 39:11	BNP RA size RIMP/MPI/Tei Index	Mortality	HR	Fair
Utsunomiya, 2009[150] Asia	Adults with chronic PH N=50 39:11	RA size	Right atrial pressure RIMP/MPI/Tei Index	Correlation	Good

Van Albada, 2008[151] Europe	Children with PAH N=29 18:11	BNP Uric acid	6MWD (absolute) 6MWD (change) Functional class Mortality Cardiac index RHC-mPAP RHC-PVR Mortality	Correlation	Good
Vizza, 2012[152] Europe	Adults with IPAH N=44 37:7	ET-1 BNP	WHO FC BNP RHC-mPAP RHC-CI RHC-PVR Clinical worsening Clinical worsening	Correlation OR	Good
Vizza, 2008[153] Europe	Adults with PAH associated with CTD N=25 21:4	Endothelin-1	BNP	Correlation	Good
Voelkel, 2000[154] US	Patients with PH N=191 NR	Uric acid	RHC-mPAP Right atrial pressure	Correlation	Good
Williams, 2006[61] UK	Adults with systemic sclerosis N=109 88:21	BNP BNP 10-fold increase baseline levels 10-fold increase baseline levels	Cardiac index RHC-mPAP RHC-PVR Right atrial pressure Mortality	Correlation HR	Fair
Wilkins, 2005[155] UK	Adults with IPAH or PAH associated with CTD N=26 21:5	RV size Cardiac index RIMP/MPI/Tei Index RA size BNP		Change in mean from baseline in response to therapy (bosentan)	Good

Yamada, 2012[156] Asia	Adults and children with IPAH N=41 29:12	BNP Uric acid	Mortality Hospitalization	HR	Good
Yanagisawa, 2012[157] Asia	Adults with PAH N=46 38:8	BNP	Mortality	HR	Good
Yang, 2012[158] Asia	Adults and children with Eisenmenger syndrome N=12 9:3	RV size mPAP		Change in mean over time in response to therapy (iloprost)	Fair
Yoshida, 2012[159] Asia	Adults with PAH N=21 18:3	BNP mPAP		Mean change from baseline in response to treatment (ambrisentan)	Fair
Zafrir, 2007[160] Asia	Adults with PPH +/- collagen vascular disease N=29 22:7	RA size RIMP/MPI/Tei Index RVEF	6MWD (absolute) Functional class 6MWD (absolute) Functional class	Correlation	Good
Zeng, 2011[161] Asia	Adults and children with IPAH N=95 61:34	BNP		Means stratified by survivor/ nonsurvivor	Good
Zhao, 2012[162] Asia	Adults and children with IPAH N=76 56:20	Uric acid	Mortality	HR	Good

Abbreviations: 6MWD=6-minute walk distance; BNP=brain natriuretic peptide; CHD=congenital heart disease; CHF=congestive heart failure; CI=cardiac index; CTD=connective tissue disease; CTEPH=chronic thromboembolic pulmonary hypertension; CVD=collagen vascular disease; DLCO=diffusion capacity of the lung for carbon monoxide; FAC=fractional area change; HR=hazard ratio; IPAH=idiopathic pulmonary arterial hypertension; mPAP=mean pulmonary artery pressure; MPI=myocardial performance index; NPV=negative predictive value; NT-proBNP=N-terminal pro-B-type natriuretic peptide; NYHA=New York Heart Association; PAH=pulmonary arterial hypertension; PH=pulmonary hypertension; PPH=primary pulmonary hypertension; PPV=positive predictive value; PVR=pulmonary vascular resistance; RA=right atrium; RHC=right heart catheterization; RIMP=right index of myocardial performance; RV=right ventricle; S'=tricuspid lateral annular systolic velocity; RVEF= right ventricular ejection fraction ; sPAP=systolic pulmonary artery pressure; SSc=systemic sclerosis; TAPSE=tricuspid annular plane systolic excursion; TDI=tissue Doppler imaging; TRV=tricuspid regurgitant jet velocity; VSD=ventricular septal defect; VTI_{RVOT}=velocity-time integral of right ventricular outflow tract

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Appendix G. Correlation Table for KQ 2

Table G-1. Correlation table for KQ 2 (management of PAH)

Andreassen, 2006[1]	NR for total cohort	Baseline	BNP	Cardiac index	61	-0.58	<0.001
			BNP	Functional class	61	0.27	0.047
			BNP	RHC-mPAP	61	0.47	<0.001
			BNP	RHC-PVR	61	0.66	<0.001
			BNP	RHC-PVR	17	0.55	0.041
			BNP	RHC-sPAP	61	-0.29	0.028
			BNP	Right atrial pressure	61	0.47	<0.001
Bendayan, 2002[2]	Mean 54.9 (Range 16 to 80)	Baseline	Uric acid	6MWD (absolute)	29	-0.35	0.03
			Uric acid	Functional class	29	0.66	0.001
			Uric acid	Mortality	29	0.66	0.001
			Uric acid	RHC-CO	29	0.06	0.72
			Uric acid	RHC-mPAP	29	0.19	0.17
Bernus, 2009[3]	Median 9.3 (Range 5.2 to 14.2)	Baseline	BNP	Cardiac index	52	-0.08	NS
			BNP	Peak TRV	47	0.23	NS
			BNP	PCWP	56	0.26	<0.05
			BNP	RHC-mPAP	57	0.16	NS
			BNP	RHC-PVR	56	0.06	NS
			BNP	Right atrial pressure	56	0.34	p<0.05
			BNP	RV size	42	0.23	NS
Borges, 2006[4]	Mean 56.4 (SD 11)	Baseline	RIMP/MPI/ Tei Index	6MWD (absolute)	37	-0.73	0.661
			RIMP/MPI/ Tei Index	RHC-PVR	37	0.172	0.47
			TAPSE	6MWD (absolute)	37	0.36	0.028
			TAPSE	RHC-PVR	37	-0.072	0.53

Campana, 2004[5]	Mean 50 (SD 11)	Baseline	BNP	Cardiac index	22	r^2=0.2 (negative correlation)	
			BNP	RHC-mPAP	22	r^2=0.1	
			BNP	Right atrial pressure	22	r^2=0.09	
			BNP	RVEF	22	r^2=0.46 (negative correlation)	
			BNP	TAPSE	22	r^2=0.005	
Cella, 2009[6]	Mean 53.8 (SD 13.1)	1 year	Change in RVSP	6MWD (change)	18	R2=0.5355	0.0006
Chin, 2007[7]	NR	Baseline	BNP	6MWD (absolute)	27	-0.59	0.04
			BNP	PCWP	27	0.32	0.10
			BNP	RHC-CO	27	-0.25	0.19
			BNP	RHC-mPAP	27	0.29	0.14
			BNP	RHC-PVR	27	0.28	0.15
			BNP	Right atrial pressure	27	0.66	<0.001
Dyer, 2006[8]	Mean 9.6 (SD 4.8)	Baseline	RIMP/MPI/ Tei Index	RHC-mPAP	12	0.94	<0.001
		Intermediate	RIMP/MPI/ Tei Index	RHC-mPAP	12	0.90	<0.001
Fahmy Elnoamany, 2007[9]	Mean 55.3 (SD 10.39)	Baseline	Endothelin-1	RHC-sPAP	53	0.94	<0.001
			sPAP	RHC-sPAP	53	0.92	<0.001
Fijalkowska, 2006[10]	Mean 41 (SD 15.1)	Baseline	BNP	6MWD (absolute)	55	-0.60	<0.001
			BNP	Cardiac index	55	-0.65	<0.001
			BNP	Functional class	55	0.45	<0.001
			BNP	Peak TRV	55	0.08	NS
			BNP	RHC-mPAP	55	0.21	NS
			BNP	RHC-PVR	55	0.43	<0.001
			BNP	Right atrial pressure	55	0.45	<0.001
Forfia, 2006[11]	Mean 55 (SD 15)	Baseline	TAPSE	RHC-PVR	63	-0.52	<0.0001

Friedberg, 2006[12]	NR	Baseline	mPAP	RHC-mPAP	17	0.85	<0.0001
			mPAP	RHC-mPAP	17	0.85	<0.0001
			sPAP	RHC-sPAP	17	0.88	<0.0001
			sPAP	RHC-sPAP	17	0.88	<0.0001
Gan, 2006[13]	Mean 48 (Range 21 to 80)	Baseline	BNP	6MWD (absolute)	30	-0.51	0.008
			BNP	Cardiac index	30	-0.45	0.019
			BNP	RHC-mPAP	30	0.28	0.143
			BNP	RHC-PVR	30	0.30	0.122
			BNP	Right atrial pressure	30	0.49	0.008
Ghofrani, 2002[14]	Mean 48.3 (SEM 3.7)	Baseline	ANP	RHC-PVR	20	0.66	<0.0001
			cGMP	RHC-PVR	36	0.139	NS
Goto, 2010[15]	Mean 64.07 (SD 12.28)	Baseline	BNP	RHC-mPAP	46	0.508	0.044
			sPAP	RHC-sPAP	46	0.505	<0.01
Grubstein, 2008[16]	Mean 52 (Range 20 to 80)	Baseline	sPAP	RHC-sPAP	38	0.6	0.001
Haddad, 2009[17]	Mean 49 (SD 11)	Baseline	mPAP	RHC-mPAP	51	0.94	0.90-0.97
			sPAP	RHC-sPAP	48	0.97	0.94-0.98
Heresi, 2010[18]	Mean 44 (SD 14)	Baseline	BNP	6MWD (absolute)	40	-0.58	<0.001
			BNP	Cardiac index	40	-0.31	0.07
			BNP	RHC-mPAP	40	0.26	0.10
			BNP	RHC-PVR	40	0.15	0.36
			BNP	Right atrial pressure	40	0.49	0.001
Heresi, 2012[19]	Mean 47 (SD 13)	Baseline	cTnI (detectable)	6MWD (absolute)	68	-0.29	0.020
				Functional class	68	0.36	0.002
				BNP	68	0.45	0.001
				RA size	68	0.36	0.010

Hinderliter, 1997[20]	NR for total cohort	Baseline	FAC	6MWD (absolute)	75	0.08	
			FAC	Cardiac index	75	-0.01	
			FAC	RHC-mPAP	75	-0.37	<0.01
			FAC	Right atrial pressure	75	-0.01	
			Pericardial effusion	6MWD (absolute)	75	-0.50	<0.01
			Pericardial effusion	Cardiac index	75	-0.40	<0.001
			Pericardial effusion	RHC-mPAP	75	0.22	
			Pericardial effusion	Right atrial pressure	75	0.50	<0.001
			RV size	6MWD (absolute)	75	-0.24	<0.05
			RV size	Cardiac index	75	-0.16	
			RV size	RHC-mPAP	75	0.25	
			RV size	Right atrial pressure	75	0.45	<0.001
			sPAP	RHC-sPAP	75	0.57	<0.001
Homma, 2001[21]	Mean 45.0 (SD 10.6)	Baseline	sPAP	RHC-sPAP	8	r^2=0.11	
Leuchte, 2005[22]	Mean 46.93 (SEM 2.8)	Mean followup 12.6 ± 1.5 months	Change in BNP	Change in 6MWD	30	-0.74	<0.001
			Change in BNP	Change in cardiac index	30	-0.49	<0.01
			Change in BNP	Change in RHC-CO	30	-0.48	<0.01
			Change in BNP	Change in RHC-mPAP	30	0.54	<0.01
			Change in BNP	Change in RHC-PVR	30	0.55	<0.01
			Change in BNP	Change in right atrial pressure	30	0.78	<0.001
Machado, 2006[23]	NR for total cohort	Baseline	BNP	6MWD (absolute)	34	-0.54	0.001
			BNP	PCWP	37	0.30	0.07
			BNP	RA size	211	0.21	0.002
			BNP	RHC-CO	37	-0.43	0.006
			BNP	RHC-dPAP	37	0.37	0.02
			BNP	RHC-mPAP	37	0.43	0.006
			BNP	RHC-PVR	37	0.51	0.001
			BNP	RHC-sPAP	37	0.59	
Machado, 2004[24]	NR for total cohort	Baseline	Nitric oxide	RHC-mPAP	12	0.56	0.054
			sPAP	RHC-sPAP	17	0.794	<0.001

Montani, 2007[25]	Mean 43.8 (Range 33.8-56.6)	Baseline	Endothelin-1	Cardiac index	33	-0.47	<0.008
			Endothelin-1	RHC-PVR	33	0.55	<0.05
			Endothelin-1	Right atrial pressure	33	0.46	0.01
Morishita, 2009[26]	Mean 32.6 (Range 15-49)	Baseline	Pericardial effusion	Functional class	7	0.34	<0.05
			RA size	Functional class	7	0.33	NS
Mukerjee, 2003[27]	Mean 57 (Range 34-80)	Baseline	BNP	RHC-mPAP	23	r^2=0.28	<0.05
			BNP	RHC-PVR	23	r^2=0.24	<0.05
Nagaya, 2000[28]	NR for total cohort	Baseline	ANP	PCWP	60	0.22	NS
			ANP	RHC-CO	60	-0.49	<0.001
			ANP	RHC-mPAP	60	0.42	<0.001
			ANP	Right atrial pressure	60	0.55	<0.001
		Baseline	BNP	PCWP	60	0.16	
			BNP	RHC-CO	60	-0.51	<0.001
			BNP	RHC-mPAP	60	0.42	
			BNP	RHC-mPAP	60	0.43	<0.05
			BNP	RHC-PVR	60	0.59	<0.001
			BNP	Right atrial pressure	60	0.55	<0.001
Nath, 2005[29]	Mean 46 (SD 11)	Long-term >1 year	Peak TRV	Functional class	20	0.26	0.29
			Peak TRV	Functional class	20	0.23	0.33
			Peak TRV	Functional class	20	0.38	0.10
Nickel, 2008[30]	Mean 47.6 (SD 15.8)	Baseline	BNP	6MWD (absolute)	139	-0.217	0.028
			BNP	Cardiac index	139	-0.378	0.001
			BNP	PCWP	139	-0.027	0.9
			BNP	RHC-PVR	139	0.321	0.006
			BNP	Right atrial pressure	139	0.283	0.008
Pyxaras, 2011[31]	Mean 55 (SD 19)	Baseline	sPAP	RHC-sPAP	60	0.457	0.002
			mPAP	RHC-mPAP	60	0.451	0.006

Souza, 2007[32]	Mean 37 (SEM 2)	Baseline	BNP	6MWD (absolute)	42	-0.31	0.052
			BNP	Cardiac index	42	-0.70	<0.001
			BNP	Functional class	42	0.81	<0.001
			BNP	RHC-mPAP	42	0.58	<0.001
			BNP	RHC-PVR	42	0.80	<0.001
			BNP	Right atrial pressure	42	0.68	0.004
Takatsuki, 2012[33]	Median 10 (Range 5-15)	Baseline	BNP	6MWD (absolute)	41	-0.32	0.04
			BNP	RHC-mPAP	47	0.34	0.02
			BNP	Right atrial pressure	45	0.48	<0.01
			BNP	RHC-PVRi	46	0.30	0.04
			BNP	RHC-CI	41	-0.22	0.16
			BNP	TRJv	69	0.36	<0.01
			BNP	WHO FC	36	0.32	0.06
			NT-proBNP	6MWD (absolute)	41	-0.49	<0.01
			NT-proBNP	RHC-mPAP	47	0.28	0.06
			NT-proBNP	Right atrial pressure	45	0.48	<0.01
			NT-proBNP	RHC-PVRi	46	0.23	0.12
			NT-proBNP	RHC-CI	41	-0.01	0.93
			NT-proBNP	TRJv	69	0.41	<0.01
			NT-proBNP	WHO FC	36	0.35	0.04
Utsunomiya, 2009[34]	Mean 46 (SD 13)	Baseline	RA size	Right atrial pressure	50	0.31	0.03
Van Albada, 2008[35]	Median 7.0 (Range 0.1-17.3)	Baseline	BNP	6MWD (absolute)	29	-0.527	<0.001
		Long-term >1 year	BNP	6MWD (change)	20	-0.63	0.04
		Baseline	BNP	Functional class	29	0.34	0.04
		Long-term >1 year	BNP	Functional class	20	0.72	0.02
		Long-term >1 year	BNP	Mortality	29	9.93	0.002
		Baseline	Uric acid	Cardiac index	16	-0.65	0.007
		Long-term >1 year	Uric acid	Mortality	29	5.93	0.015
		Baseline	Uric acid	RHC-mPAP	16	0.63	0.01
		Baseline	Uric acid	RHC-PVR	16	0.71	0.03

Vizza, 2012[36]	Mean 53 (SD 17)	Baseline	ET-1	WHO FC	44	0.35	0.02
				BNP	44	0.51	0.001
				RHC-mPAP	44	0.38	0.01
				RHC-CI	44	-0.43	0.004
				RHC-PVR	44	0.48	0.001
Voelkel, 2000[37]	NR for total cohort	Baseline	Uric acid	RHC-mPAP	191	0.41	<0.0001
			Uric acid	Right atrial pressure	191	0.486	<0.0001
Williams, 2006[38]	Mean 60 (SD 11)	Baseline	BNP	Cardiac index	68	-0.5	<0.0001
			BNP	RHC-mPAP	68	0.62	<0.0001
			BNP	RHC-PVR	68	0.81	<0.0001
			BNP	Right atrial pressure	68	0.53	<0.0001
Zafrir, 2007[39]	Mean 51 (SD 14.7)	Baseline	RA size	6MWD (absolute)	29	-0.42	0.02
				Functional class	29	0.39	0.04
			RIMP/MPI/ Tei Index	6MWD (absolute)	29	-0.25	0.18
			RVEF	Functional class	29	-0.45	0.019

Abbreviations: 6MWD=6-minute walk distance; ANP=A-type natriuretic peptide; BNP=B-type natriuretic peptide ; CO=cardiac output; CVD=collagen vascular disease; FAC=fractional area change; mPAP=mean pulmonary artery pressure; MPI=myocardial performance index; NR=not reported; PCWP=pulmonary capillary wedge pressure; PVR=pulmonary vascular resistance; RA=right atrium; RIMP=right index of myocardial performance; RV=right ventricle; RVEF=right ventricular ejection fraction; SD=standard deviation; SEM=standard error of the mean; sPAP=systolic pulmonary artery pressure; TAPSE=tricuspid annular plane systolic excursion; TRV=tricuspid regurgitant jet velocity

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