Comparative Effectiveness Review
Number 9

Comparative Effectiveness of Percutaneous Coronary Interventions and Coronary Artery Bypass Grafting for Coronary Artery Disease

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Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the State Children's Health Insurance Program (SCHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting Comparative Effectiveness Reviews of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

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 are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see http://effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that Comparative Effectiveness Reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence.

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 e-mail list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly.

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Background

Atherosclerosis develops in a patchy, discontinuous fashion within coronary arteries. Therefore, it is possible to treat the discrete areas of obstruction that most impede coronary blood flow to the myocardium. The mechanical approaches to coronary revascularization fall broadly into two categories: coronary artery bypass grafting surgery (CABG) and catheter-based percutaneous coronary interventions (PCI). Together, these coronary revascularization methods are among the most common major medical procedures performed in North America and Europe.

Coronary bypass surgery and coronary angioplasty (with or without stents) are alternative approaches to mechanical coronary revascularization, so their comparative effectiveness in terms of patient outcomes has been of great interest. The comparative effectiveness of bypass surgery and angioplasty is an open question primarily for those patients for whom either procedure would be technically feasible and whose coronary disease is neither too limited nor too extensive.

CABG is generally preferred for patients with left main coronary artery disease or severe triple-vessel disease with reduced left ventricular function because it has been previously shown in randomized trials to improve survival compared with medical therapy. In contrast, PCI is generally preferred for patients with most forms of single-vessel disease when symptoms warrant coronary revascularization, in light of its lower procedural risk and the evidence that PCI reduces angina and myocardial ischemia in this subset of patients.

The choice between PCI and CABG is most relevant for patients whose coronary artery disease (CAD) lies in between these extremes, namely patients with single-vessel disease of the proximal left anterior descending artery (LAD), most forms of double-vessel CAD, and less extensive forms of triple-vessel CAD. Most randomized controlled clinical trials (RCTs) of angioplasty and surgery have been conducted in this middle segment of the patient population with CAD.

The purpose of this report is to evaluate the evidence for the comparative effectiveness of PCI and CABG in this population of patients with CAD. Specifically, the report addresses the following key questions:

Key Question 1a. In patients with ischemic heart disease and angiographically proven single or multi-vessel disease, what is the effectiveness of PCI compared with CABG in reducing the occurrence of adverse objective outcomes and improving subjective outcomes?

Key Question 1b. Over what period of time are the comparative benefits of PCI and CABG sustained?

Key Question 2. Is there evidence that the comparative effectiveness of PCI and CABG varies based on:

a. Age, sex, race, or other demographic risk factors?

b. Coronary disease risk factors, diabetes, or other comorbid disease?

c. Angiographic-specific factors including, but not limited to, the number of diseased vessels amenable to bypass or stenting, vessel territory of stenoses (e.g., left main or anterior descending coronary arteries, right coronary artery, circumflex coronary artery), diffuse vs. focal stenoses, left ventricular function, or prior revascularization procedures?

d. CABG-specific factors including, but not limited to, cardiopulmonary bypass mode (normothermic vs. hypothermic), type of cardioplegia used (blood vs. crystalloid), or use of saphenous vein grafts, single or bilateral internal mammary artery grafts, or other types of bypass grafts?

e. Clinical presentation (e.g., stable angina or unstable angina based on New York Heart Association functional class I-IV, acute coronary syndrome, cardiogenic shock, acute myocardial infarction with or without ST elevation, or silent ischemia)?

f. Adjunctive medical therapies, such as short-term intravenous or oral antiplatelet drugs, or long-term use of oral antiplatelet drugs?

g. Process characteristics such as provider volume, hospital volume, and setting (e.g., academic vs. community)?

h. Prior PCI or CABG revascularization procedures?

Conclusions

We identified 23 RCTs of PCI vs. CABG that enrolled a total of 9,963 patients. (Descriptions and full names of RCTs are shown in Tables A and B.) The early studies (patient entry 1987-1993) principally used balloon angioplasty as the PCI technique, and the recent studies (1994-2002) principally used stents as the PCI technique. Only one small trial of PCI vs. CABG used drug-eluting stents (Seoul-Hong). The demographic characteristics and cardiac risk factor profiles of trial participants were typical of patients with coronary disease, although only 27 percent of trial patients were women and few trials included patients age 75 and over. Patients with either left main disease, single-vessel disease other than in the proximal LAD, prior CABG, or poor left ventricular function were generally excluded. Among PCI-assigned patients, use of stents and adjunctive medical therapy (e.g., dual antiplatelet therapy) was common in the recent studies but not in the earlier trials conducted when balloon angioplasty was standard. Arterial grafting with the left internal mammary artery was frequently employed in CABG-assigned patients, especially in more recent trials. The quality of most trials was high; all but two trials included randomization methods that were sound and clearly explained, their dropout rates were low, and they performed intention-to-treat analyses.

To assess the extent to which the RCT results are generalizable to the wider population of patients presenting with CAD, we evaluated the results of 96 articles reporting on patients who received either PCI or CABG and were followed in 10 large registries. Overall the quality of the observational studies was high because each enrolled large numbers of subjects who had good followup and adequate descriptions of most key subject characteristics. Among the registries, patients with single-vessel disease were more likely to be selected for PCI, whereas patients with left main or extensive triple-vessel disease or total coronary occlusions were more likely to be selected for CABG.

Short-term/procedural outcomes

For consistency, throughout this document, we present results in the positive frame (e.g., survival rather than mortality, freedom from strokes rather than strokes, etc.). We present PCI-CABG survival differences and PCI-CABG differences in freedom from myocardial infarction (MI), stroke, angina, and repeat revascularization such that positive numbers favor PCI and negative numbers favor CABG. Similarly, we present PCI/CABG odds ratios such that ratios greater than 1.0 favor PCI and ratios less than 1.0 favor CABG. In this section, we present the short-term/procedural outcomes which were reported either as "in hospital," "procedural," or "within 30 days" of the procedure. Results were statistically homogeneous, unless otherwise noted.

Procedural survival. In randomized trials, procedural survival was high for both procedures and did not differ significantly: PCI-CABG procedural survival difference was 0.1 percent (95-percent confidence interval (CI): -0.3 to +0.6 percent) and PCI/CABG odds ratio for survival of 1.4 (CI: 0.98 to 1.97). There were no significant differences in procedural survival when trials were subdivided into balloon-era and stent-era studies or into single-vessel disease and multi-vessel disease patient populations.

In large registries, procedural survival has increased significantly over time. Short-term procedural survival after PCI generally exceeded that of CABG in both earlier and more recent time intervals, however, even after controlling for differences in clinical characteristics.

Freedom from procedural strokes. Freedom from procedural stroke (reported by 16 randomized trials) was significantly higher after PCI than after CABG: PCI-CABG difference in freedom from procedural stroke of 0.6 percent (CI: 0.2 to 1.0 percent, p=0.002) and PCI/CABG odds ratio for freedom from procedural stroke 1.96 (CI: 1.16, 3.3, p=0.01).

Freedom from procedural myocardial infarctions. Freedom from procedural MI was not assessed in a consistent fashion across trials of PCI and CABG, and there was significant heterogeneity in this outcome among the randomized trials. The pooled PCI-CABG difference in freedom from procedural MI was small and not statistically significant.

Long-term outcomes

Survival. Long-term survival across all randomized trials between 1 and 5 years of followup was similar in CABG-assigned and PCI-assigned patients, with less than 1-percent

absolute PCI-CABG survival difference at each time point. (PCI/CABG odds ratios ranged from 0.94 to 1.13.) None of the differences was statistically significant.

The long-term survival difference between PCI and CABG was significantly different in the older trials that relied on balloon angioplasty, but not in the more recent trials that employed coronary stents. The 5-year survival was higher after CABG in balloon-era trials (PCI-CABG survival difference -2.1 percent, CI: -4.1 to -0.1 percent, p=0.04), whereas 5-year survival did not differ between the procedures in stent-era trials (PCI-CABG survival difference 1.1 percent, CI: -1.4 to +3.7 percent). Stent-era trials included more patients with single-vessel disease, however, and had shorter followup than balloon-era trials.

In large clinical registries, comparative survival after PCI or CABG varied significantly according to the extent of coronary disease. Survival was significantly better after PCI in patients with single-vessel disease that did not involve the proximal LAD, and survival was significantly better after CABG in patients with extensive triple-vessel or left main disease. In analyses from large clinical registries of patients with middle spectrum CAD severity, there was no difference in survival after PCI or CABG.

Freedom from angina. Freedom from angina was significantly greater after CABG than after PCI in randomized trials between 1 and 5 years post-procedure. (PCI-CABG difference in freedom from angina ranged from -5.0 percent to -8.0 percent; PCI/CABG odds ratio ranged from 0.50 to 0.66, $p<0.0001$ at 1, 3, and 5 years.)

Freedom from repeat revascularization. Freedom from repeat coronary revascularization was significantly greater after CABG than after PCI. (PCI-CABG difference in freedom from repeat revascularization ranged from -23 to -33 percent, PCI/CABG odds ratios ranged from 0.11 to 0.13; $p <0.0001$ at 1 and 5 years.) The gap between PCI and CABG in repeat revascularization procedures narrowed in more recent trials that used coronary stents. Nevertheless, patients undergoing PCI with stents required repeat procedures significantly more often than patients undergoing CABG.

Freedom from myocardial infarction. The PCI-CABG difference in freedom from MI was small, less than 1 percent (PCI/CABG odds ratios ranged from 0.87 to 0.92), between 1 and 5 years after the procedure and did not achieve statistical significance at any time point.

Quality of life. Eleven randomized trials reported quality-of-life data using a variety of different measures. In general, quality-of-life scores improved to a significantly greater extent after CABG than after PCI between 6 months and 3 years of followup but equalized thereafter. The degree of improvement in quality of life was correlated with relief of angina.

Cost. The methods of cost determination varied among trials and countries, yet 9 of the 10 RCTs found that the initially lower cost among PCI-assigned patients narrowed substantially over followup. In medium to long-term followup, PCI-assigned patients had only modestly lower costs (roughly 5 percent) than CABG-assigned patients. This pattern of progressively narrowing cost differences was evident both in trials employing balloon angioplasty and in trials using coronary stents.

Comparative effectiveness by patient demographics

In contrast to the fairly robust evidence concerning overall clinical outcomes, there was much less evidence from randomized trials to gauge whether the comparative effectiveness of CABG and PCI varies according to patient or provider characteristics. Most clinical trials have not reported outcomes in key subgroups and most have reported only survival, not other outcomes. The most extensively examined subgroup (patients with diabetes) was reported by only 7 of 23 randomized trials. Furthermore, the selection of patients and providers to participate in trials narrowed the range of clinical characteristics and reduced the statistical power to detect variations. For example, most patients in RCTs had preserved left ventricular function, so variations in the efficacy of PCI and CABG according to ventricular function would be difficult to detect. Nevertheless, some conclusions can be drawn from the evidence provided by randomized trials and large registries.

Age. Older patients had more procedural complications from both PCI and CABG, especially stroke. Patients aged 65 years and older had lower long-term survival compared with younger patients. The survival difference between PCI and CABG at 7 years in the BARI trial did not significantly favor CABG in the older patients (-4.7 percent PCI-CABG survival difference) to a greater extent than in the younger patients (-2.8 percent PCI-CABG survival difference). Older patients had more freedom from angina, however, and more freedom from repeat revascularization procedures. The randomized trials enrolled very few patients 75 years of age and over, so conclusions about the comparative effectiveness of PCI and CABG cannot be made for very old patients.

Gender. Roughly 27 percent of the patients in randomized trials were women, and their outcomes were similar to those among men in the trials that examined outcomes by gender. In the BARI trial, women had lower overall survival than men with each procedure, but the PCI-CABG survival difference in women was similar to that in men. In the pooled data from four stent-era trials (ARTS, ERACI-II, MASS-II, SoS), women had clinical outcomes relatively similar to those of men.

Race. Outcomes after PCI and CABG according to race were analyzed only by the BARI trial and registry, which found African-American patients had significantly lower overall survival, irrespective of treatment with PCI or CABG.

Comparative effectiveness by comorbidities

Diabetes. Survival at 1 and 5 years in patients with diabetes was reported by six trials (Figure A). The BARI trial reported a significant survival advantage for patients with diabetes assigned to CABG: 5-year survival of 80 percent with CABG vs. 65 percent with PCI. None of the other trials found as dramatic a difference in survival between patients with and without diabetes. In the EAST trial, for example, the 59 patients with treated diabetes had slightly better survival in the PCI arm at 3 years, equivalent survival at 5 years, and slightly better survival in the CABG arm at 8 years. Among the 62 patients with diabetes in the RITA trial, however, only 2 of the 29 PCI patients died, compared with 8 of the 33 CABG patients. Overall, the survival difference between PCI and CABG was not significantly different among patients with diabetes

(Figure A); the pooled PCI-CABG survival difference was -0.8 percent at 5 years, but the confidence limits were very wide, from -8.3 to +6.6 percent (PCI/CABG odds ratio 0.87; CI: 0.51 to 1.49).

Obesity. In general, obesity was not consistently associated with significant differences in comparative effectiveness of PCI and CABG in the two trials that reported outcomes by body mass index. Overall rates of survival, freedom from MI, and freedom from stroke were not affected by body mass index in the ARTS trial. Survival in the BARI trial was decreased in patients with either a very low (<20) or a very high (≥35) body mass index.

Other comorbidities. Outcomes according to hypertension, tobacco use, renal dysfunction, and vascular disease were not generally reported by randomized trials.

Comparative effectiveness by angiographic factors

Extent of disease. There was no significant difference in the comparative survival benefit when randomized trials were subdivided into those enrolling patients with single-vessel proximal LAD disease and those enrolling patients with multi-vessel disease (Figure B). In the RITA trial, the survival difference between PCI and CABG was comparable in patients with single-vessel disease and multi-vessel disease (mostly two-vessel disease).

In the randomized trials that enrolled patients with multi-vessel disease, the survival difference between CABG and PCI was greater among patients with three-vessel disease than among patients with two-vessel disease but did not achieve statistical significance. The randomized trials generally excluded patients with extensive coronary disease. Accordingly, comparative efficacy of CABG and PCI according to variations in coronary anatomy could not be fully tested.

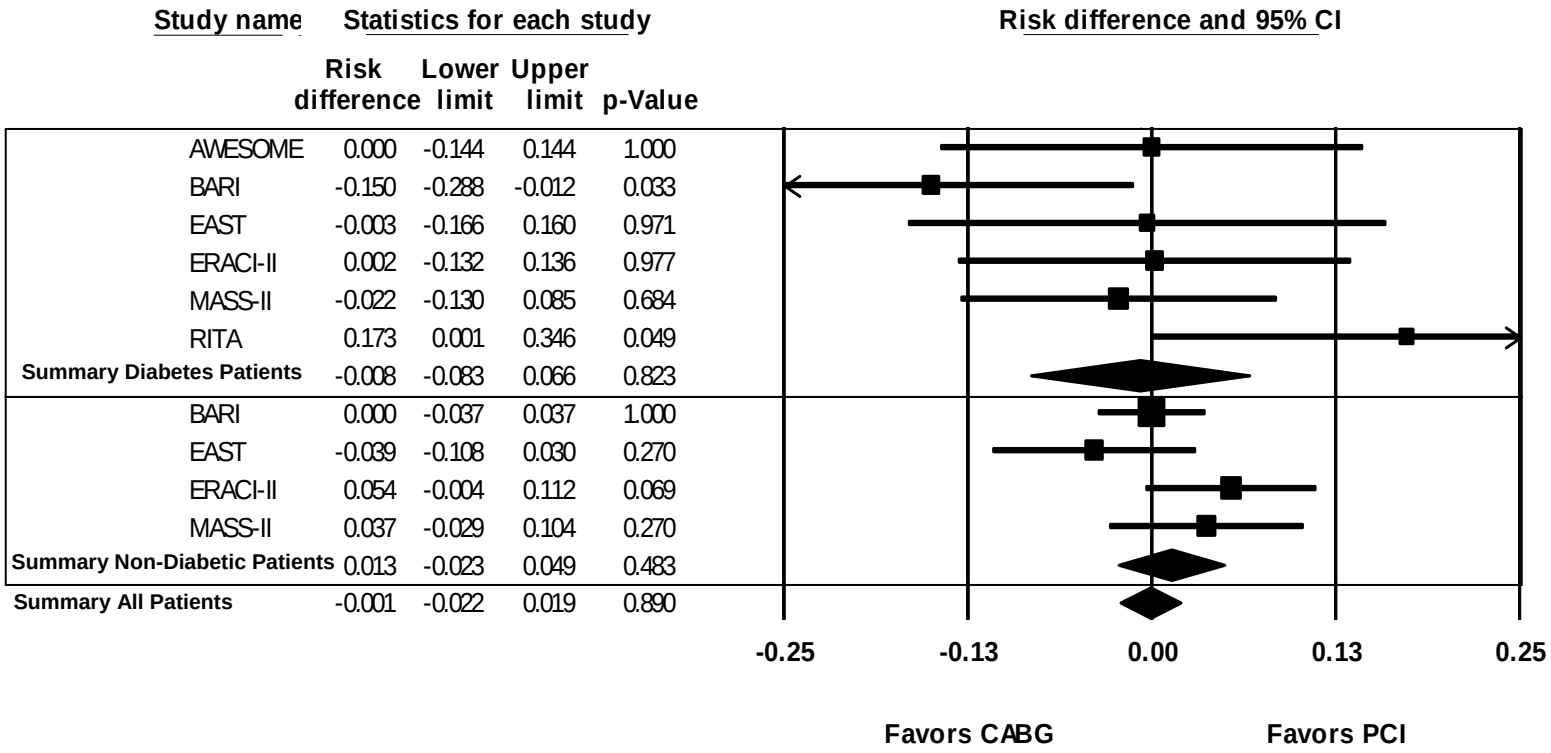
In large clinical registries, comparative survival after PCI or CABG varied significantly with the extent of coronary disease, with better survival after PCI in patients with the least extensive coronary disease and better survival after CABG in patients with the most extensive disease.

Left ventricular function. Most trials comparing PCI and CABG randomized patients with relatively preserved left ventricular function and a low prevalence of heart failure. The limited range of ejection fractions within the trials precludes a stringent test of whether the comparative effectiveness of PCI and CABG varies according to left ventricular function. Only the BARI and AWESOME trials reported specific analyses: they found no significant differences in the comparative efficacy of PCI and CABG according to the level of left ventricular function.

Comparative effectiveness by CABG-specific factors

Use of minimally invasive techniques. "Minimally invasive" surgery, which is performed through a small throracotomy incision on a beating heart, was compared with PCI in eight small randomized trials. These trials enrolled patients with single-vessel proximal LAD disease (predominantly or exclusively) and generally used PCI with stents as the comparator. These trials showed no significant differences in survival between PCI and CABG over a relatively short followup period.

Figure A. Comparison of survival among patients with and without diabetes at 5 years

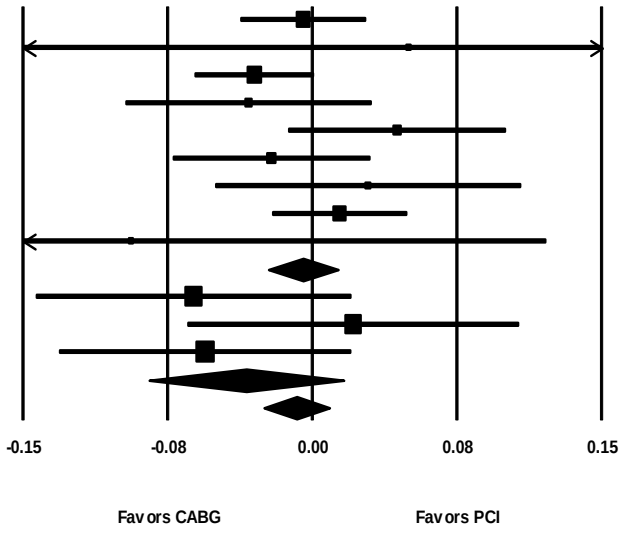


Patients with diabetes: Heterogeneity statistics: Q=8.4; p-value = 0.14; I^2=40. PCI/CABG odds ratio: 0.87 (CI: 0.51, 1.49; p=0.6).
Patients without diabetes: Heterogeneity statistics: Q=5.0; p-value = 0.2; I^2=40. PCI/CABG odds ratio: 1.16 (CI: 0.75, 1.78; p=0.5).

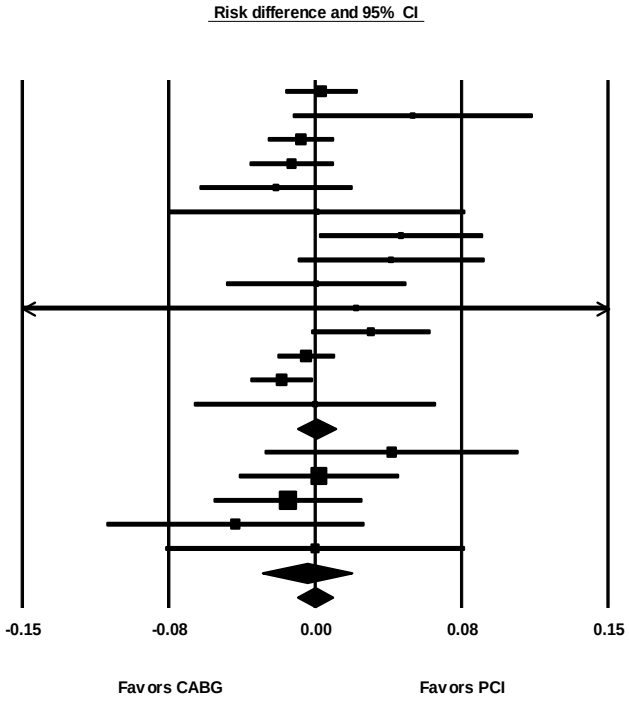
Note: All studies reporting comparative effectiveness data for patients with diabetes were included in this analysis, not just the studies reporting comparative outcomes for patients with and without diabetes.
Abbreviations: CABG=coronary artery bypass grafting; CI=confidence interval; PCI=percutaneous coronary intervention.

Figure B. Comparison of single (SVD) with multi-vessel (MVD) survival at 1 and 5 years

Study name	Risk difference	Lower limit	Upper limit	p-Value	PCI	CABG
ARTS	-0.005	-0.037	0.028	0.780	504 / 552	513 / 559
AWESOME	0.050	-0.166	0.266	0.649	30 / 38	19 / 26
BARI	-0.030	-0.061	0.001	0.059	727 / 842	768 / 860
EAST	-0.033	-0.097	0.031	0.312	153 / 174	161 / 177
ERACI II	0.044	-0.013	0.101	0.128	194 / 209	176 / 199
GABI*	-0.021	-0.072	0.030	0.421	161 / 173	148 / 156
MASS-II	0.029	-0.050	0.108	0.475	149 / 177	139 / 171
RITA	0.014	-0.021	0.049	0.428	455 / 494	438 / 483
Toulouse	-0.094	-0.309	0.121	0.393	21 / 31	27 / 35
	-0.005	-0.023	0.013	0.587	2393 / 2690	2390 / 2666
Lausanne	-0.062	-0.143	0.020	0.141	59 / 65	63 / 65
Leipzig	0.021	-0.065	0.107	0.629	95 / 106	91 / 104
MASS	-0.056	-0.131	0.020	0.151	65 / 71	67 / 69
	-0.034	-0.085	0.016	0.180	219 / 242	221 / 238
	-0.008	-0.025	0.009	0.335	2612 / 2932	2611 / 2904



Study name	Risk difference	Lower limit	Upper limit	p-Value	PCI	CABG
ARTS	0.003	-0.015	0.022	0.731	570 / 585	571 / 588
AWESOME	0.050	-0.012	0.112	0.111	189 / 208	175 / 203
BARI*	-0.007	-0.024	0.010	0.408	879 / 915	884 / 914
CABRI	-0.012	-0.034	0.010	0.278	511 / 532	491 / 505
EAST	-0.020	-0.059	0.019	0.318	181 / 191	184 / 190
ERACI	0.001	-0.075	0.077	0.984	59 / 62	58 / 61
ERACI II	0.044	0.002	0.086	0.041	216 / 223	196 / 212
GABI	0.039	-0.009	0.087	0.111	151 / 155	130 / 139
MASS-II	0.001	-0.046	0.047	0.980	183 / 194	181 / 192
Myoprotect	0.021	-0.239	0.281	0.874	16 / 21	14 / 19
Octostent	0.029	-0.002	0.059	0.068	138 / 138	136 / 140
RITA*	-0.005	-0.019	0.010	0.547	497 / 506	489 / 495
SoS	-0.017	-0.033	-0.001	0.037	464 / 476	492 / 496
Toulouse*	-0.000	-0.062	0.062	0.999	70 / 73	68 / 71
	0.000	-0.009	0.010	0.936	4126 / 4279	4071 / 4225
Groningen	0.039	-0.026	0.104	0.238	51 / 51	47 / 49
Leipzig*	0.002	-0.039	0.043	0.925	107 / 110	103 / 106
MASS	-0.014	-0.052	0.024	0.476	70 / 71	70 / 70
Poland	-0.041	-0.107	0.025	0.227	47 / 49	50 / 50
Seoul-Kim	0.000	-0.077	0.077	1.000	48 / 50	48 / 50
	-0.004	-0.027	0.018	0.705	323 / 331	318 / 325
	-0.000	-0.009	0.009	0.940	4450 / 4610	4389 / 4550



Note: Trial names followed by an asterisk indicate that the survival data were abstracted from Kaplan-Meier curves.
Abbreviations: CABG=coronary artery bypass grafting; CI=confidence interval; PCI=percutaneous coronary intervention.

Use of internal mammary arteries. Standard CABG was used in all trials that enrolled patients with multi-vessel disease, with variable use of left internal mammary grafting, ranging from a low of 37 percent in the early GABI study to over 90 percent in the more recent ARTS, MASS-II, and SoS studies. In a meta-regression, the 1-year survival advantage for CABG vs. PCI increased along with the proportion of internal mammary artery grafts used, but this trend was not statistically significant and not evident at 5 years.

Comparative effectiveness by clinical presentation

Three randomized trials (ARTS, BARI, and SoS) examined the outcomes of patients according to their clinical presentation. Comparative survival after PCI and CABG was not consistently different between patients with stable or unstable angina. The randomized trials generally excluded patients with acute myocardial infarction, severe congestive heart failure, or cardiogenic shock, so no conclusions about the comparative efficacy of PCI and CABG can be drawn for these patient subgroups.

Comparative effectiveness and use of adjunctive medical therapies

The RCTs did not report comparative effectiveness data based on the use of adjunctive medical therapy for PCI or CABG. It is uncertain whether patients who have undergone CABG are as likely as patients who have undergone PCI to comply with recommendations for long-term use of aspirin, beta-blockers, angiotensin-converting enzyme inhibitors, and statins. There is relatively little evidence on this question from randomized trials; however, the Duke Database, a large observational registry of patients receiving both procedures, reports relatively similar use of evidence-based therapies after PCI and CABG.

Comparative effectiveness and volume-outcome relationship

There was considerable evidence that procedural outcomes of both CABG and PCI were significantly worse in low-volume hospitals and with low-volume operators. This relationship remained significant for PCI, even as procedural risk has been reduced by the availability of coronary stents and adjunctive therapy. While none of these studies were randomized and causality is uncertain, these findings are consistent with a large body of literature demonstrating a relationship between the volume of patients treated and short-term survival for a wide variety of procedures. The magnitude of association of procedural outcomes with volume of PCI and CABG may be only modest, however, at least among sufficiently experienced centers and operators.

Comparative effectiveness and prior revascularization

Most randomized trials excluded patients with prior CABG, but one randomized trial and several clinical registries have compared PCI with re-do CABG in patients with a prior CABG. In the AWESOME trial, 142 patients with prior CABG were randomized to either re-do CABG (75 patients) or PCI (67 patients). While procedural survival was significantly lower in the patients assigned to CABG (92 vs. 100 percent), 3-year survival did not differ significantly. A

similar pattern has been reported by large clinical registry studies from Cleveland, Emory, and Kansas City: procedural mortality was higher for re-do CABG than for PCI, but survival at 5 to 6 years of followup did not differ significantly.

Remaining Issues

This comprehensive review of the comparative effectiveness of PCI and CABG identified numerous gaps in evidence that would be suitable for future research. The paucity of published analyses of PCI and CABG outcomes according to patient characteristics strongly suggests the value of a collaborative pooling of individual patient-level data from the randomized trials to (a) enhance statistical power to identify subgroup effects and (b) reduce publication bias by including data from all trials. A collaboration of four stent trials (ARTS, ERACI-II, MASS-II, and SoS) has pooled 1-year outcomes and provided useful short-term analysis in key subgroups. The planned extension of this collaborative pooling to include 5-year followup data should be very informative.

A more extensive collaborative study to pool individual patient data from both balloon-era and stent-era trials would provide additional advantages. First, the number of patients and outcome events would be greatly increased, thereby improving statistical power even further in patient subgroups. Second, more direct assessments of the impact of stents on the comparative effectiveness of PCI and CABG would be feasible, as well as assessment of whether relative efficacy changes over extended followup.

Further research on the association of procedure volume with outcome should examine additional outcome measures, both short term (e.g., nonfatal myocardial infarction, completeness of revascularization) and long term (e.g., survival, angina relief, freedom from repeat procedures), preferably in large patient cohorts using contemporaneous CABG and PCI and applying the same analytic methods. Development of evidence-based process measures for PCI and CABG would facilitate efforts to improve quality of care and might provide better performance measures than procedure volume. However, research is required to understand the relative ability of structural measures (e.g., volume) and process measures to predict institutions or physicians with low-quality CABG and PCI outcomes.

Further clinical trials are also needed to assess whether the availability of drug-coated stents has affected the comparative efficacy of PCI and CABG. Such trials are particularly warranted, as pooled studies suggest that rates of survival and MI are not different between bare metal stents and drug-coated stents over medium-term followup. Recent safety concerns about drug-coated stents emphasize the need for extended followup and trials large enough to detect clinically meaningful differences in outcomes. Furthermore, the procedural risk of CABG in large registries has also declined progressively over time, indicating that both CABG and PCI methods continue to evolve. Several trials to compare contemporary CABG with PCI using drug-coated stents, including the large FREEDOM (NCT 00086540) and SYNTAX trials (NCT 00114972), are currently underway and should be complete in 2012.[a]

[a] NCT numbers are National Clinical Trial numbers, which the National Institutes of Health assign to trials for tracking purposes.

Table A. Brief overview of reviewed randomized controlled trials

AMIST—Angioplasty versus Minimally Invasive Surgery Trial
A small United Kingdom trial of 100 patients with single-vessel proximal LAD disease conducted 1999-2001.

Reeves BC, Angelini GD, Bryan AJ, et al. A multi-centre randomised controlled trial of minimally invasive direct coronary bypass grafting versus percutaneous transluminal coronary angioplasty with stenting for proximal stenosis of the left anterior descending coronary artery. Health Technol Assess 2004 Apr;8(16):1-43.

ARTS—Arterial Revascularization Therapies Study
A large European trial of 1,205 patients with MVD that used bare metal stents. One of four trials that participated in the pooling project of stent trials.

Serruys PW, Unger F, Sousa JE, et al. Comparison of coronary-artery bypass surgery and stenting for the treatment of multivessel disease. N Engl J Med 2001 Apr 12;344(15):1117-24.

AWESOME—Angina With Extremely Serious Operative Mortality Evaluation
A medium-sized U.S Department of Veterans Affairs trial of 454 patients with medically refractory angina, high procedural risk, and single or multi-vessel disease.

Morrison DA, Sethi G, Sacks J, et al. Percutaneous coronary intervention versus coronary artery bypass graft surgery for patients with medically refractory myocardial ischemia and risk factors for adverse outcomes with bypass: a multicenter, randomized trial. Investigators of the Department of Veterans Affairs Cooperative Study #385, the Angina With Extremely Serious Operative Mortality Evaluation (AWESOME). J Am Coll Cardiol 2001 Jul;38(1):143-9.

BARI—Bypass Angioplasty Revascularization Investigation
Large U.S.-Canadian trial of 1,829 patients that used balloon angioplasty and reported extensively on outcomes in patient subgroups. Extended followup to 10 years has been reported.

The Bypass Angioplasty Revascularization Investigation (BARI) Investigators. Comparison of coronary bypass surgery with angioplasty in patients with multivessel disease. N Engl J Med 1996 Jul 25;335(4):217-25.

CABRI—Coronary Angioplasty versus Bypass Revascularisation Investigation
Large European trial of 1,054 patients with MVD that used balloon angioplasty and had limited followup.

CABRI Trial Participants. First-year results of CABRI (Coronary Angioplasty versus Bypass Revascularisation Investigation). Lancet 1995 Nov 4;346(8984):1179-84.

EAST—Emory Angioplasty versus Surgery Trial
A medium-sized, single-center U.S. trial of 392 patients with MVD that used balloon angioplasty and reported extended followup to 8 years.

King SB, 3rd, Lembo NJ, Weintraub WS, et al. A randomized trial comparing coronary angioplasty with coronary bypass surgery. Emory Angioplasty versus Surgery Trial (EAST). N Engl J Med 1994 Oct 20;331(16):1044-50.

ERACI-I—Argentine Randomized Trial of PTCA versus CABG in Multi-Vessel Disease
A small Argentine trial of 127 patients with MVD that used balloon angioplasty and had limited followup.

Rodriguez A, Boullon F, Perez-Balino N, et al. for ERACI Group. Argentine randomized trial of percutaneous transluminal coronary angioplasty versus coronary artery bypass surgery in multivessel disease (ERACI): in-hospital results and 1-year follow-up. J Am Coll Cardiol 1993;22(4):1060-7.

ERACI-II—Second Argentine Randomized Trial of PTCA versus CABG in Multi-Vessel Disease
A medium-sized trial of 450 patients with MVD conducted by the same Argentine group that organized ERACI-I. The trial used bare metal stents and was one of four trials that participated in the primary data pooling project.

Rodriguez A, Bernardi V, Navia J, et al. for ERACI II Investigators. Argentine Randomized Study: Coronary Angioplasty with Stenting versus Coronary Bypass Surgery in Patients with Multiple-Vessel Disease (ERACI II): 30-day and one-year follow-up results. J Am Coll Cardiol 2001 Jan;37(1):51-8.

GABI—German Angioplasty Bypass Surgery Investigation
A medium-sized German trial of 359 patients with MVD that used balloon angioplasty and has reported the longest followup of any PCI-CABG trial (13 years).

Hamm CW, Reimers J, Ischinger T, et al. A randomized study of coronary angioplasty compared with bypass surgery in patients with symptomatic multivessel coronary disease. German Angioplasty Bypass Surgery Investigation (GABI). N Engl J Med 1994 Oct 20;331(16):1037-43.

Table A. Brief overview of the RCTs (continued)

Groningen
A small, single-center Dutch study of 100 patients with single-vessel proximal LAD disease randomized to either stent implantation or minimally invasive bypass surgery.

Drenth DJ, Veeger NJGM, Winter JB, et al. A prospective randomized trial comparing stenting with off-pump coronary surgery for high-grade stenosis in the proximal left anterior descending coronary artery: three-year follow-up. J Am Coll Cardiol 2002 Dec 4;40(11):1955-60.

Lausanne
A small, single-center Swiss trial of 134 patients with single-vessel proximal LAD disease that used balloon angioplasty.

Goy JJ, Eeckhout E, Burnand B, et al. Coronary angioplasty versus left internal mammary artery grafting for isolated proximal left anterior descending artery stenosis. Lancet 1994;343(8911):1449-53.

Leipzig
A small, single-center German study of 220 patients with single-vessel proximal LAD disease that compared bare-metal stents with minimally invasive CABG.

Diegeler A, Thiele H, Falk V, et al. Comparison of stenting with minimally invasive bypass surgery for stenosis of the left anterior descending coronary artery. N Engl J Med 2002 Aug 22;347(8):561-6.

MASS-I—Medicine, Angioplasty, or Surgery Study
A small, single-center Brazilian trial that used three treatment options for patients with single-vessel proximal LAD disease. (Only outcomes in patients assigned to PCI or CABG were used in this report.)

Hueb WA, Bellotti G, de Oliveira SA, et al. The Medicine, Angioplasty, or Surgery Study (MASS): a prospective, randomized trial of medical therapy, balloon angioplasty or bypass surgery for single proximal left anterior descending artery stenoses. J Am Coll Cardiol 1995;26(7):1600-5.

MASS-II—Second Medicine, Angioplasty, or Surgery Study
A medium-sized Brazilian trial of 408 patients with MVD conducted by the same investigators as the MASS-I trial. This study used bare-metal stents and was one of four trials that contributed to the primary data pooling project for stent trials.

Hueb W, Soares PR, Gersh BJ, et al. The Medicine, Angioplasty, or Surgery Study (MASS-II): a randomized, controlled clinical trial of three therapeutic strategies for multivessel coronary artery disease: one-year results. J Am Coll Cardiol 2004 May 19;43(10):1743-51.

Myoprotect I
A small, single-center German trial of 44 high-risk patients with left main or left main equivalent disease randomized to PCI supported by retroinfusion of the anterior cardiac vein or to bypass surgery.

Pohl T, Giehrl W, Reichart B, et al. Retroinfusion-supported stenting in high-risk patients for percutaneous intervention and bypass surgery: results of the prospective randomized Myoprotect I study. Catheter Cardiovasc Interv 2004;62(3):323-30.

Octostent
A medium-sized Dutch trial of 280 patients with single-vessel or multi-vessel disease comparing coronary stents with off-pump bypass surgery.

Eefting F, Nathoe H, van Dijk D, et al. Randomized comparison between stenting and off-pump bypass surgery in patients referred for angioplasty. Circulation 2003 Dec 9;108(23):2870-6.

Poland
A small, single-center Polish trial of 100 patients with single-vessel proximal LAD disease comparing coronary stenting with minimally invasive direct coronary bypass grafting.

Cisowski M, Drzewiecki J, Drzewiecka-Gerber A, et al. Primary stenting versus MIDCAB: preliminary report – comparison of two methods of revascularization in single left anterior descending coronary artery stenosis. Ann Thorac Surg 2002;74(4):S1334-9.

RITA—Randomised Intervention Treatment of Angina
A large United Kingdom trial of 1,011 patients with single-vessel or multi-vessel disease comparing balloon angioplasty with bypass surgery.

Henderson RA, Pocock SJ, Sharp SJ, et al. Long-term results of RITA-1 trial: clinical and cost comparisons of coronary angioplasty and coronary-artery bypass grafting. Randomised Intervention Treatment of Angina. Lancet 1998 Oct 31;352(9138):1419-25.

Table A. Brief overview of the RCTs (continued)

Seoul-Hong
A small, single-center Korean trial of 189 patients with proximal LAD disease comparing treatment with DES to MIDCAB.

Hong SJ, Lim D-S, Seo HS, et al. Percutaneous coronary intervention with drug-eluting stent implantation vs. minimally invasive direct coronary artery bypass (MIDCAB) in patients with left anterior descending coronary artery stenosis. Catheter Cardiovasc Interv 2005 Jan;64(1):75-81.

Seoul-Kim
A small, single-center Korean trial of 100 patients with proximal LAD disease comparing treatment with BMS to MIDCAB.

Kim JW, Lim DS, Sun K, et al. Stenting or MIDCAB using ministernotomy for revascularization of proximal left anterior descending artery? Int J Cardiol 2005 Mar 30;99(3):437-41.

SIMA—Stenting versus Internal Mammary Artery study
A small European trial of 123 patients with isolated proximal LAD disease comparing coronary stenting with MIDCAB.

Goy JJ, Kaufmann U, Goy-Eggenberger D, et al. A prospective randomized trial comparing stenting to internal mammary artery grafting for proximal, isolated de novo left anterior coronary artery stenosis: the SIMA trial. Mayo Clin Proc 2000;75(11):1116-23.

SoS—Stent or Surgery
A large European-Canadian trial of 988 patients with MVD comparing coronary stenting with CABG. One of four trials that contributed to the individual data pooling project for stent trials.

SoS Investigators. Coronary artery bypass surgery versus percutaneous coronary intervention with stent implantation in patients with multivessel coronary artery disease (the Stent or Surgery trial): a randomised controlled trial. Lancet 2002 Sep 28;360(9338):965-70.

Toulouse
A small, single-center French study of 152 patients with single-vessel proximal LAD disease comparing balloon angioplasty with bypass surgery.

Carrie D, Elbaz M, Puel J, et al. Five-year outcome after coronary angioplasty versus bypass surgery in multivessel coronary artery disease: results from the French Monocentric Study. Circulation 1997;96(9 Suppl):II-1-6.

Abbreviations: BMS=bare-metal stent; CABG=coronary artery bypass grafting; DES=drug-eluting stent; LAD=left anterior descending artery; MIDCAB=minimally invasive direct coronary artery bypass grafting; PCI=percutaneous coronary intervention; PTCA=percutaneous transluminal coronary angioplasty.

Table B. Summary of comparative effectiveness data for PCI vs. CABG

Key Questions and outcomes	Strength of evidence[a]	Summary, conclusions, and comments
Key Question 1a: Comparative effectiveness objective outcomes and subjective outcomes		
Short-term outcomes		
Procedural survival	Acceptable	- Reported by 23 RCTs. - Procedural survival was slightly but not significantly higher in PCI patients (PCI-CABG survival difference 0.1%; 95%CI: -0.3 to +0.6%. - Procedural survival in RCTs was higher than that reported by large administrative databases and clinical registries.
Freedom from procedural stroke	Acceptable	- Reported by 14 RCTs. - Freedom from procedural strokes was significantly more common after PCI (PCI-CABG difference in freedom from procedural stroke 0.6%; CI: 0.2 to 1.0%; p=0.01).
Freedom from procedural MI	Weak	- Reported by 20 RCTs. - Definition of MI varied across trials; results were heterogeneous. - Freedom from procedural MI was slightly but not significantly lower after CABG.
Long-term outcomes		
Survival	Robust	- Overall survival in RCTs was slightly higher after CABG than after PCI between 1 and 5 years of followup, but the absolute PCI-CABG survival difference was small at each time point (less than 1%) and not statistically significant. - 5-year survival was significantly higher after CABG in balloon-era trials (PCI-CABG survival difference -2.1%; CI: -4.1 to -0.1%). However, in stent-era trials, 5-year survival was not significantly different (PCI-CABG survival difference 1.1%; CI: -1.4 to +3.7%). - There was no significant difference in the PCI-CABG survival difference according to extent of disease.
Freedom from angina	Robust	- Reported by 12 RCTs at 1 year and 7 RCTs at 3 and 5 years. - Freedom from angina was significantly greater after CABG (PCI-CABG difference in freedom from angina ranges from -5% to -8%; p value <0.0001 at 1, 3, and 5 years).
Freedom from repeat revascularization	Robust	- Reported by 11 RCTs at 1 year and 9 RCTs at 5 years - Patients assigned to PCI required 24% more repeat procedures than patients assigned to CABG at 1 year (p <0.0001) and 33% more at 5 years (p<0.0001).
Freedom from myocardial infarction	Acceptable	- 10 RCTs reported followup data. - There was no difference in freedom from MI between PCI and CABG.
Quality of life	Acceptable	- Reported by 11 RCTs using a variety of different measures. - Quality-of-life scores improved significantly more after CABG than after PCI between 1 and 3 years. - Quality-of-life scores were correlated with the presence and severity of angina.
Cost	Robust	- Reported by 10 RCTs using a variety of methods. - 9 RCTs found significantly lower initial costs for PCI than for CABG, but this difference narrowed substantially over subsequent followup.
Key Question 1b: Sustainability of comparative effectiveness		
Survival	Acceptable	- 11 trials (including 77% of all randomized patients) reported 5 or more years of followup. - The PCI-CABG survival difference in these 11 trials did not change significantly between 1 and 5 years. - 4 trials with longer followup showed no major changes in the PCI-CABG survival difference between 5 and 7 to 8 years of followup.
Freedom from angina	Acceptable	- The initial significant advantage of CABG over PCI in freedom from angina grew progressively smaller between 1 year and 5 years of followup.

Table B. Summary of comparative effectiveness data for PCI versus CABG (continued)

Key Questions and Outcomes	Strength of Evidence	Summary, Conclusions, and Comments
Key Question 2a. Comparative effectiveness by demographic factors		
Age	Acceptable	- Outcomes by age reported by 3 studies. - There were more procedural complications, especially stroke, in the older patients. - Patients aged 65 years and older had lower overall survival. - The RCTs enrolled very few patients age 75 and over, limiting conclusions about the comparative effectiveness of PCI and CABG in this population.
Gender	Acceptable	- Outcomes by gender reported by 3 studies. - Women had lower overall survival, but the survival difference between PCI and CABG was similar to that in men. -Women had lower quality of life at baseline but improved to a similar degree with CABG and PCI.
Race	Weak	- Outcomes by race reported by only 1 study. - African-American patients had a lower survival regardless of PCI or CABG treatment.
Key Question 2b. Comparative effectiveness by comorbidities		
Diabetes	Acceptable	- Survival at 1 and 5 years in patients with diabetes was reported by 6 RCTs. - The BARI trial found significantly better survival for patients with diabetes assigned to CABG (5-year survival of 80% vs. 65%). - None of the other five reports found a significant difference in survival between PCI and CABG for patients with diabetes. -The pooled data from all trials showed no significant difference in survival after PCI vs. after CABG (PCI-CABG survival difference -0.8%; CI: -8.3 to +6.6%).
Obesity	Weak	- Obesity did not consistently alter the comparative effectiveness of PCI and CABG.
Other comorbidities	Weak	- There was no evidence suggesting that hypertension, tobacco use, renal dysfunction, and vascular disease increased risk differently among PCI and CABG recipients.
Key Question 2c. Comparative effectiveness by angiographic factors		
Extent of disease	Acceptable	- There was no significant difference by extent of disease among patients assigned to PCI or CABG. - In clinical registries, patients with extensive disease had improved survival with CABG, whereas patients with minimal disease had improved survival with PCI. (Interaction test was highly significant.)
Left ventricular function	Weak	- Few patients with poor left ventricular function were enrolled in RCTs. - There was no evidence that the PCI-CABG survival difference was modified by the degree of left ventricular dysfunction.
Use of stents	Acceptable	- 10 trials used bare-metal stents, 11 used balloon angioplasty, and only the Seoul trial used drug-eluting stents. - Survival at 5 years was significantly better after CABG in balloon-era trials, but there was no difference in survival in stent-era trials.
Key Question 2d. Comparative effectiveness by CABG-specific factors		
Use of minimally invasive techniques	Weak	- "Minimally invasive" surgery has been compared with PCI in 7 small RCTs. - These trials showed similar outcomes after PCI and CABG over a relatively short followup period.
Use of mammary arteries	Weak	- Internal mammary artery use increased over time.
Key Question 2e. Comparative effectiveness by clinical presentation		
Clinical presentation	Acceptable	- Reported by 3 RCTs. - Comparative survival after PCI and CABG was not consistently different between patients with stable or unstable angina.

Table B. Summary of comparative effectiveness data for PCI versus CABG (continued)

Key Questions and Outcomes	Strength of Evidence	Summary, Conclusions, and Comments
Key Question 2f. Comparative effectiveness by adjunctive therapies		
Adjunctive therapies	Weak	- RCTs did not provide comparative effectiveness data based on the use of adjunctive medical therapy for PCI or CABG.
Key Question 2g. Comparative effectiveness by process characteristics		
Process characteristics	Robust	- Short-term procedural risk of both CABG and PCI increased significantly in low-volume hospitals and with low-volume operators.
Key Question 2h. Comparative effectiveness by prior revascularization		
Prior revascularization	Weak	- 1 RCT and several clinical registries have compared PCI with re-do CABG in patients with a prior CABG. - Procedural risk was considerably higher in CABG patients assigned to CABG, but there is no difference in late survival.

[a]Strength of evidence was based on predefined criteria, as defined by the GRADE methodology.

Abbreviations: CABG=coronary artery bypass grafting; CI=confidence interval; MI=myocardial infarction; PCI=percutaneous coronary intervention; RCT= randomized controlled trial.

Introduction

Background

Since atherosclerosis develops in a patchy, discontinuous fashion within the coronary artery, it is possible to address therapeutically the discrete areas of obstruction that most impede coronary blood flow to the myocardium. The mechanical approaches to coronary revascularization fall broadly into two categories: coronary artery bypass grafting surgery (CABG) and catheter-based percutaneous coronary interventions (PCI). Together, these coronary revascularization techniques are among the most common major medical procedures performed in North America and Europe. In 2004, there were 249,000 CABGs and 664,000 PCI procedures performed in the United States alone.[1] There has been considerable interest in the effects of coronary revascularization procedures on patient outcomes, and especially upon the circumstances in which one procedure should be preferred over the other.

Coronary bypass surgery was first described in 1967 by Kolessov, who performed anastomoses of the left internal mammary artery to the left anterior descending artery in patients with a beating heart.[2] Later that year, Favaloro at the Cleveland Clinic introduced the most common technique of CABG by constructing a bypass graft using a saphenous vein conduit.[3] The initial technique consisted of the anastamosis of a segment of saphenous vein to the aorta and to the coronary artery beyond the most severely narrowed segment, thereby "bypassing" the obstruction. The techniques for coronary artery bypass graft (CABG) surgery have been progressively refined over the past four decades, based on incremental improvements in the operation itself, in cardiac anesthesia, in post-operative care, and in concomitant medical therapy. The most important improvement was the use of arterial grafts as conduits rather than saphenous veins whenever feasible – the left internal mammary artery (LIMA) to the left anterior descending (LAD) in particular is recognized as a superior approach.[4] More recently, there has been great interest in returning to operative techniques that avoid the use of the cardiopulmonary bypass machine, or that use a smaller thoracotomy incision rather than a full sternum splitting operation, or both.[5] These newer approaches to CABG, which aim to achieve the same level of coronary revascularization as the standard operation but with less trauma and fewer adverse effects, are under active development.

Coronary angioplasty was developed by Gruntzig in 1977 at the University of Zurich as an alternative approach to coronary bypass surgery.[6, 7] The use of a balloon-tipped catheter to dilate localized areas of coronary obstruction was a revolutionary paradigm shift in cardiovascular medicine. The technique of angioplasty has also undergone progressive refinement over the past three decades as a result of better catheters, improved imaging, and new adjunctive medical therapy during and after the procedure. The major limitation of angioplasty has been restenosis – the tendency of the dilated coronary segment to constrict during healing, such that blood flow is again impeded several weeks to months after the initial procedure. Restenosis developed after 30% to 40% of balloon angioplasty procedures, typically within six months, leading to a repeat revascularization procedure. Many drugs were tried to prevent restenosis, but none was effective. The key improvement was the development of the coronary stent, an expandable metal mesh tube that buttresses the dilated segment and limits restenosis. Randomized clinical trials

(RCTs) showed that bare metal coronary stents reduced significantly the rate of angiographic restenosis and of repeat revascularization procedures. However, these trials also showed that stents had no effect on the rate of death or of acute myocardial infarction compared with balloon angioplasty.[8] Contemporary stents now coat the metal meshwork with drugs (e.g., sirolimus, paclitaxel) that reduce cellular proliferation in response to the injury of dilatation. Randomized trials comparing drug-coated stents with bare metal stents showed a further reduction in the rate of repeat revascularization by the drug-coated stent but no reduction in the rates of death or myocardial infarction.[9] Reducing restenoses may not reduce death or myocardial infarctions, however, because restenosis is usually a slow process that rarely leads to acute obstruction and serious cardiac events.[9] Recent evidence suggests that drug-coated stents may be associated with higher long-term rates of stent thrombosis and late myocardial infarction, especially after dual antiplatelet therapy is discontinued.[10]

Comparative Efficacy of CABG and PCI

In large clinical series, there are clear differences between the patients selected for PCI and for CABG. Coronary anatomy determines the technical feasibility of PCI[11, 12] and CABG,[13, 14] and PCI is often infeasible in patients with extensive disease or chronic total occlusions. In large clinical series, most patients with single-vessel disease are treated with PCI, whereas most patients with triple-vessel disease or left main disease are referred for CABG. The comparative effectiveness of bypass surgery and angioplasty is an open question primarily for those patients in which both procedures are technically feasible and whose coronary disease is neither too limited nor too extensive. This middle segment of the spectrum of CAD includes single-vessel disease of the proximal LAD, most forms of double-vessel CAD, and less extensive forms of triple-vessel CAD. This group of patients provides real treatment options for clinicians and the equipoise needed for randomization in clinical trials. Most comparative studies of angioplasty and surgery have been conducted in this segment of the patient population with CAD.

The effects of coronary revascularization can be assessed using many outcome measures. This comparative effectiveness review focuses on patient-centered outcomes rather than laboratory measures, since clinical outcomes evident to the patient are the most pertinent to the choice between angioplasty and surgery. The most important outcomes are the serious, irreversible clinical complications: death, myocardial infarction, and stroke. Other important outcomes are symptoms (especially angina), functional capacity, quality of life, employment, cost, and cognitive function. Finally, the durability of the revascularization procedure is important to patients – will a repeat revascularization procedure be needed, and if so, which one and when?

It is important to emphasize that these outcomes span several dimensions and the effect of a therapy need not be consistent across them. Coronary stents, as discussed above, reduce the need for repeat revascularization procedures, but have not been shown to reduce myocardial infarction or death. Thus, the comparative effectiveness of CABG and PCI must be assessed separately for the various clinical outcomes of interest.

Systematic overviews of trials comparing CABG and PCI have been conducted previously.[15-18] Additional data have become available since their publication, both new trials and additional reports with long-term outcomes from included trials. The previous systematic overviews generally focused on a limited set of outcomes and did not address efficacy in subgroups.

Variations in Effectiveness

One of the major issues in applying evidence from the medical literature to medical decisions is the question of generalizability: Namely, are the results of formal randomized studies a reliable guide to the likely results for a given patient treated in the local hospital? The reason this question is pertinent is that the outcomes of treating a disease may well vary according to characteristics of the patient, the details of the therapy itself, and the setting in which therapy is provided. The key questions we address in this report are predicated upon the hypothesis that the comparative effectiveness of bypass surgery and angioplasty may well vary according to these factors.

It is important to distinguish the different circumstances under which the effectiveness of therapy may vary according to patient characteristics. The first possibility is that the therapy is generally effective for certain well-defined groups of patients, but is ineffective or even harmful for other well-defined groups of patients. In the case of coronary revascularization, for instance, neither angioplasty nor surgery is likely to improve the outcomes of a patient with a single coronary occlusion that has led to complete myocardial infarction of the distal myocardium. Groups of patients who have no realistic expectation of benefit from treatment are generally not enrolled in clinical studies, as it would be unethical to expose them to a risky procedure. The more common question is whether, among patients who have some reasonable expectation of benefit from therapy, the benefit varies in a predictable fashion and with a magnitude great enough that the choice of therapy is affected. Here it is important to distinguish between variations in the "relative risk reduction" and "absolute risk differences" as measures of the magnitude of benefit from therapy. Most clinical studies report results as relative risk reductions (or similar measures such as odds ratios or hazard ratios). A therapy that reduces relative risk by 25 percent across all subgroups of patients is conventionally said to show a consistent therapeutic effect across subgroups.[19] Some degree of variation in relative risk reduction is common in clinical trials, but statistically significant variation in relative risk reduction across subgroups (assessed using the treatment-by-covariate interaction test) is distinctly unusual. For instance, the time delay in administering fibrinolytic therapy for acute MI significantly affects relative risk reductions achieved (p for interaction = 0.002), but fibrinolytic therapy yields similar relative risk reductions in patients with or without diabetes, and in men and women.[20] Nevertheless, patient subgroups may differ in the "absolute risk difference" from therapy despite equivalent "relative risk reductions." While both measures have advantages, absolute risk differences are more pertinent to clinical decisions since they better reflect the increased chance of a better outcome from the choice of one therapy over the alternative therapy.

Throughout this report we present absolute risk differences whenever possible, since these risks are of the greatest interest to patients. (We did calculate both relative and absolute risk difference between the procedures and found no significant differences between these metrics).

Scope and Key Questions

The purpose of this report is to answer the following key questions:

Key Question 1a. In patients with ischemic heart disease, and angiographically-proven single or multi-vessel disease, what is the comparative effectiveness of PCI compared to CABG, in reducing the occurrence of adverse objective outcomes and improving subjective outcomes?

Key Question 1b. Over what period of time are the comparative benefits of PCI and CABG sustained?

For the purposes of answering these key questions, we provide the following definitions: PCI includes percutaneous coronary angioplasty (PTCA), with or without drug-eluting stents (DES) or bare metal stents (BMS). CABG includes traditional on-pump or off-pump bypass procedures; on-pump or off-pump minimally invasive procedures; and CABG with transmyocardial revascularization (TMR). Long-term and short-term *objective* outcomes refer to outcomes that impact patients' health, including, but not limited to, peri-procedural death or complications, non-fatal myocardial infarctions, congestive heart failure, stroke, nosocomial infections, respiratory failure or other pulmonary complications, acute or chronic renal failure, cardiac arrhythmias, and long-term survival and event-free survival (major adverse cardiac events). Long-term and short-term *subjective* outcomes refer to outcomes that impact patients' perceived quality of life, functional health status, or general health status. Subjective outcomes may include, but are not limited to, freedom from angina, functional angina classification, cognitive impairment, productivity, and functional capacity. Intermediate outcomes may also be considered if available evidence clearly links such outcomes to long-term or short-term outcomes. These include completeness of revascularization, target lesion revascularization, restenosis following PCI, CABG graft closure, the need for secondary revascularization procedures, readmission within 30 days, readmission within 6 months, and post-procedure discharge to rehabilitation facilities.

Key Question 2. Is there evidence that the comparative effectiveness of PCI and CABG varies based on:

a. Age, sex, race, or other demographic risk factors?

b. Coronary disease risk factors, diabetes, or other comorbid disease?

c. Angiographic-specific factors including, but not limited to, the number of diseased vessels amenable to bypass or stenting, vessel territory of stenoses (e.g., left main or anterior coronary arteries, right coronary artery, circumflex coronary artery), diffuse vs. focal stenoses, left ventricular function, or prior revascularization procedures?

d. CABG-specific factors including, but not limited to, cardiopulmonary bypass mode (normothermic vs. hypothermic), type of cardioplegia used (blood vs. crystalloid), or use

of saphenous vein grafts, single or bilateral internal mammary artery grafts, or other types of bypass grafts?

e. Clinical presentation (e.g., stable angina or unstable angina, based on NYHA functional class I-IV, acute coronary syndrome, cardiogenic shock, acute myocardial infarction with or without ST elevation, or silent ischemia)?

f. Adjunctive medical therapies, such as short-term intravenous or oral antiplatelet drugs, or long-term use of oral antiplatelet drugs?

g. Process characteristics such as provider volume, hospital volume, and setting (e.g., academic vs. community)?

h. Prior PCI or CABG revascularization procedures?

Methods

Topic Development

The topic for this report was nominated in a public process. With input from technical experts, the Scientific Resource Center for the AHRQ Effective Health Care Program drafted the initial key questions and, after approval from AHRQ, posted them to a public Web site. The public was invited to comment on these questions. After reviewing the public commentary, the Scientific Resource Center drafted final key questions and submitted them to AHRQ for approval.

Search Strategy

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. Appendix A provides the details of our search strategies. We did not limit the searches to the English language.

To identify randomized controlled trials comparing PCI and CABG, we used terms such as *angioplasty*, *coronary*, and *coronary artery bypass surgery*. We also manually searched the reference lists of included articles, conference abstracts, and the bibliographies of expert advisors.

To complement the RCT data, we searched for observational data for two purposes—to evaluate the generalizability of the RCT results and to address key questions left unanswered by the RCTs. To evaluate the generalizability of the RCT results, we first identified relevant comparative registries of patients receiving PCI or CABG through discussion with expert advisors. We then sought articles describing the demographics and outcomes of interest for registry patients. We identified additional comparative registries through our literature search for RCTs and from additional, limited MEDLINE® and internet searches. The Scientific Resource Center also conducted a MEDLINE® search for additional studies from the registries already identified and for additional registries.

To identify systematic reviews, we searched MEDLINE®, the Cochrane Database of Systematic Reviews, and the Web sites of the National Institute for Clinical Excellence, Guidelines.gov, and the NHA Health Technology Assessment Programme. We used results from previously conducted meta-analyses and systematic reviews when appropriate.

To further address key question 2g, additional articles on the volume-outcomes association were identified from previous systematic reviews,[21-23] a technical report on the development of the AHRQ Quality Indicators,[24] and subsequent unpublished updates obtained from the authors on CABG and PCI volume indicators.

The Effective Health Care program is dedicated to identifying as many studies as possible that are relevant to the questions for each of its comparative effectiveness reviews. In order to do

so, pharmaceutical and device industry stakeholders are systematically requested to provide information regarding their products (e.g. details of studies conducted). Industry is often most familiar with the existence of scientific data concerning their products – in particular, they know of scientific data, protocols, and methodology that may not have made its way into the published literature. The Scientific Resource Center performed a search of the US Food and Drug Administration website for the original manufacturers of the devices relevant to the key questions for this report. A request for information was subsequently sent to the manufacturers, which included the following: a current product label, published and unpublished randomized controlled trials and observational studies relevant to the clinical outcomes.

Study Selection

We developed criteria for inclusion and exclusion based on the patient populations, interventions, outcome measures, and types of evidence specified in the key questions. We retrieved full-text articles of potentially relevant abstracts and conducted a second review for inclusion by reapplying the inclusion criteria. Results published only in abstract form were not included in our analyses.

Interventions of Interest. As outlined under key question 1, we included a variety of PCI technologies including balloon angioplasty, with or without stents. Similarly, we included traditional on-pump or off-pump bypass procedures and on-pump or off-pump minimally invasive procedures.

Outcomes of Interest. The short- and long-term objective outcomes of interest included survival, event-free survival, non-fatal myocardial infarctions, congestive heart failure, stroke, nosocomial infections, respiratory failure or other pulmonary complications, renal failure, cardiac arrhythmias, other procedural complications, and costs. Additionally, we were interested in short- and long-term subjective outcomes including quality of life, freedom from angina, cognitive impairment, productivity, and functional capacity. We were also interested in intermediate outcomes including completeness of revascularization, target lesion revascularization, restenosis following PCI, CABG graft closure, the need for secondary revascularization procedures, readmission rates, and post-procedure discharge to rehabilitation facilities.

Study Designs of Interest. We sought RCTs that compared PCI and CABG in patients with angiographically-proven CAD. We included all such comparative RCTs without limitation by subject population, year, or type of surgical or percutaneous intervention. For a RCT to be included, at least one article describing that RCT had to report at least one of the objective outcomes. Because the primary aim of this report was to evaluate the comparative effectiveness of the two procedures, we excluded RCTs that compared two or more PCI technologies that did not also include a CABG arm. Similarly, we excluded RCTs that compared two or more CABG technologies that did not also include a PCI arm. Finally, we excluded trials that compared either PCI with medical therapy or CABG with medical therapy, unless the trial involved a three-way randomization to PCI, CABG, and medical therapy and reported a randomized comparison of PCI with CABG.

For observational studies addressing either the generalizability of the RCT data or to address key questions left unanswered by the RCT data, we included studies from clinical or

administrative databases with at least 1000 recipients of each of the revascularization procedures. We also included observational studies from registries that compared at least 1000 PCI recipients with at least 1000 CABG recipients. To be included, articles of observational studies had to provide sufficient information about the patient populations (e.g., demographics, pre-procedure coronary anatomy, and co-morbid conditions) and procedures performed (e.g., balloon angioplasty versus bare metal stent versus drug-eluting stent types) for us to be able to compare these populations with those included in the RCTs. Also, the observational studies had to report on the outcomes and populations of interest as defined in our key questions.

To determine whether RCTs or observational studies met inclusion criteria, two authors independently reviewed the title, abstract, and full text (as necessary). Conflicts between reviewers were resolved through re-review and discussion.

Data Extraction

We extracted the following data from the included trials: study design; setting; population characteristics (e.g., sex, age, ethnicity, co-morbid conditions, coronary anatomy); eligibility and exclusion criteria; detailed information about the PCI and CABG interventions performed (including adjunctive medical therapies provided post-procedure); numbers of patients screened, eligible, enrolled, and lost to follow-up; method of outcome ascertainment; and results for each outcome. Data were abstracted by two authors independently onto pre-tested data forms (Appendix E). Data abstraction conflicts were resolved by re-review and discussion with other authors.

Because we were interested in both short-term and long-term comparative outcomes, we extracted all the available survival data for PCI and CABG in 30-day intervals post-procedure. For those studies that provided overall survival data in the form of Kaplan-Meier survival curves, we extracted the data directly from the curves as follows: we imported each survival curve figure into Microsoft Paint and created separate figures for PCI and CABG data. We then removed all extraneous information from each figure (e.g., extra lines, words, figure legends) and saved the files in .jpeg format. We exported the .jpeg files into DigitizeIt software (http://digitizer.sourceforge.net/) that enabled us to specify the axes (x=time, y=percent surviving). The software algorithm provides the maximal x/y coordinates for each survival curve. We exported these curves into Microsoft Excel and reduced each dataset to 12 points per year (i.e., monthly data). We then visually checked these data by comparing them to the survival data reported in the text of the article.

For the observational studies, we abstracted the same demographic/baseline characteristic variables as for the RCTs. For key question 2g, we also abstracted information about hospital and clinician volume levels analyzed in each study, methods of risk adjustment, and outcomes assessed. Given concerns about potential biases in the non-RCT data, we did not abstract comparative outcomes of PCI and CABG from the registries that were not adjusted for key baseline population characteristics (e.g., unadjusted mortality).

Quality Assessment of Individual Studies

We used predefined criteria to assess the quality of included trials and observational studies based primarily on the CONSORT statement[25, 26] of reporting for RCTs relevant to the two procedures of interest. Specifically, we considered the method of randomization, the use of intention-to-treat analysis, the report of drop out rates, and the extent to which valid outcomes were described. Blinding and related criteria are less relevant measures of quality for RCTs in which one set of patients receives a surgical procedure and another set of patients does not.

To assess the quality of the observational studies of the registries, we evaluated the extent to which they reported adequate baseline characteristics about the included population and the extent to which valid outcomes were described adjusted for the baseline characteristics.

We applied a three-category quality grading system (A, B, C) to both RCT and observational studies (Table 1) as has been utilized by several prior AHRQ comparative effectiveness reviews.[27, 28] An assigned grade to a study of one design is not equivalent to the same grade for a study of a different design. This grading system does not attempt to assess the comparative validity of studies across different design strata. For example, a "B" rated RCT is not judged to have the same methodological quality as a "B" rated observational study. Thus, both study design and quality grade should be considered when interpreting the methodological quality of a study.

Table 1. Criteria for grading included studies

Quality Grade for Included Studies	Criteria
A (good)	Study has the least bias and results are considered valid. It 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; analyze and report results.
B (fair/moderate)	Study is susceptible to some bias, but probably not sufficient to invalidate the results. It 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.
C (poor)	Study has 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.

Grading the Body of Evidence for Each Key Question

We assigned an overall grade describing the body of evidence for each key question utilizing the GRADE system as described by Guyatt and colleagues (Table 2).[29] Specifically, the grade is based on the number and quality of individual studies, duration of follow-up, the consistency across studies, magnitude of effects, applicability, the likelihood of publication bias, and (especially for the observational studies) the potential influence of plausible confounders.

The grades provide a shorthand description of the strength of evidence supporting the major questions we addressed. However, they may oversimplify the many complex issues involved in appraising a body of evidence. The individual studies involved in formulating the composite grade differed in their design, reporting, and quality. As a result, the strengths and weaknesses of the individual studies addressing each key question should also be considered, as described in detail in the text, tables, and figures.

Table 2. Criteria for grading the body of evidence for each key question

Quality GRADE for Body of Evidence	Criteria
Robust	There is a high level of assurance with validity of the results for the key question based on at least two high quality studies with long-term follow-up of a relevant population. There is no important scientific disagreement across studies in the results for the key question.
Acceptable	There is a good to moderate level of assurance with validity of the results for the key question based on fewer than two high quality studies or in high quality studies that lack long-term outcomes of relevant populations. There is little disagreement across studies in the results for the key question.
Weak	There is a low level of assurance with validity of results for the key question based on either moderate to poor quality studies or on studies of a population that may have little direct relevance to the key question. There could be disagreement across studies in the results for the key question.

Data Synthesis

To evaluate the comparative effectiveness of PCI and CABG at 1-month, 6-months, 12-months, 24-months, 36-months, and 60-months post-procedures, we computed two summary effects for each outcome of interest at each of these time intervals using random effects models: summary risk differences and summary odds ratios. To calculate the effects sizes for each study at each time interval for each outcome of interest, we calculated the proportion of patients with the outcome of interest, p_{PCI}, (e.g., survival) and a variance for this outcome $p_{PCI}\, q_{PCI}\, /n$ (where q=1-p and n is the sample size) for the PCI patients. We repeated this for the CABG patients. We calculated the risk difference effect size as p_{PCI}-p_{CABG}. We calculated the odds ratio effect size as $(p_{PCI}/q_{PCI})/(p_{CABG}/q_{CABG})$.[a] We performed these calculations using Comprehensive Meta-Analysis software (version 2).

There remains considerable debate in the literature regarding the best metric to use to calculate treatment effects for data from 2 x 2 tables—a detailed discussion of the advantages of different effect size metrics has been published.[31, 32] Throughout the text, we present the summary risk differences as the primary outcome metric because several of the outcomes of interest (e.g., procedural mortality) were rare events and the risk difference is a more stable outcome metric than odds ratios under this circumstance.[31, 32] Additionally, it is a readily clinically interpretable measure. We note that we found consistent results between these two outcome metrics.

[a] We did not calculate the Mantel-Haenszel estimator of the odds ratio because it cannot be used with a random effects model. We did not calculate the Peto estimator of the odds ratio because it has been shown to be a potential biased estimator that can produce both over- and underestimates of the underlying parameters.[30, 31]

For consistency, we adopted the following conventions for presenting the results: we present the summary risk difference as a percent difference, all outcomes were calculated in their "positive frame" (e.g., survival rather than mortality, freedom from angina rather than angina, etc.), and all of the forest plots are oriented such that the studies on the left of the origin favor CABG and those to the right of the origin favor PCI. We present PCI-CABG risk differences such that positive numbers favor PCI and negative numbers favor CABG. Similarly, we present PCI/CABG odds ratios such that ratios greater than 1.0 favor PCI and ratios less than 1.0 favor CABG.

To evaluate the association between the number of mammary artery grafts and survival, we performed meta-regression using the number of subjects randomized for weighting the predictor variables and the risk difference in survival between PCI and CABG as the dependent variable. We performed these calculations using SPSS 11.01.

To minimize heterogeneity, we synthesized only those studies describing similar interventions in similar populations. We performed formal assessments of heterogeneity for summary effects and present the Chi^2 statistic for heterogeneity. Additionally, we calculated the I^2 statistic measuring the extent of inconsistency among the studies' results—which is interpreted as the approximate proportion of total variation in study estimates that is due to heterogeneity rather than sampling error[33] and considered I^2 statistics in excess of 50% to be heterogeneous. For those analyses in which we found heterogeneity among the included studies, we performed sensitivity analysis to explore the effects of individual studies on reported summary effects by removing each study individually. Additionally, we re-calculated separate summary effect size for the balloon-era and stent-era trials and for the single-vessel and multi-vessel trials.

We sought evidence of publication bias by evaluating the association between the sample size of a study and the likelihood of that study reporting statistically significant outcomes by visual inspection of funnel plots.

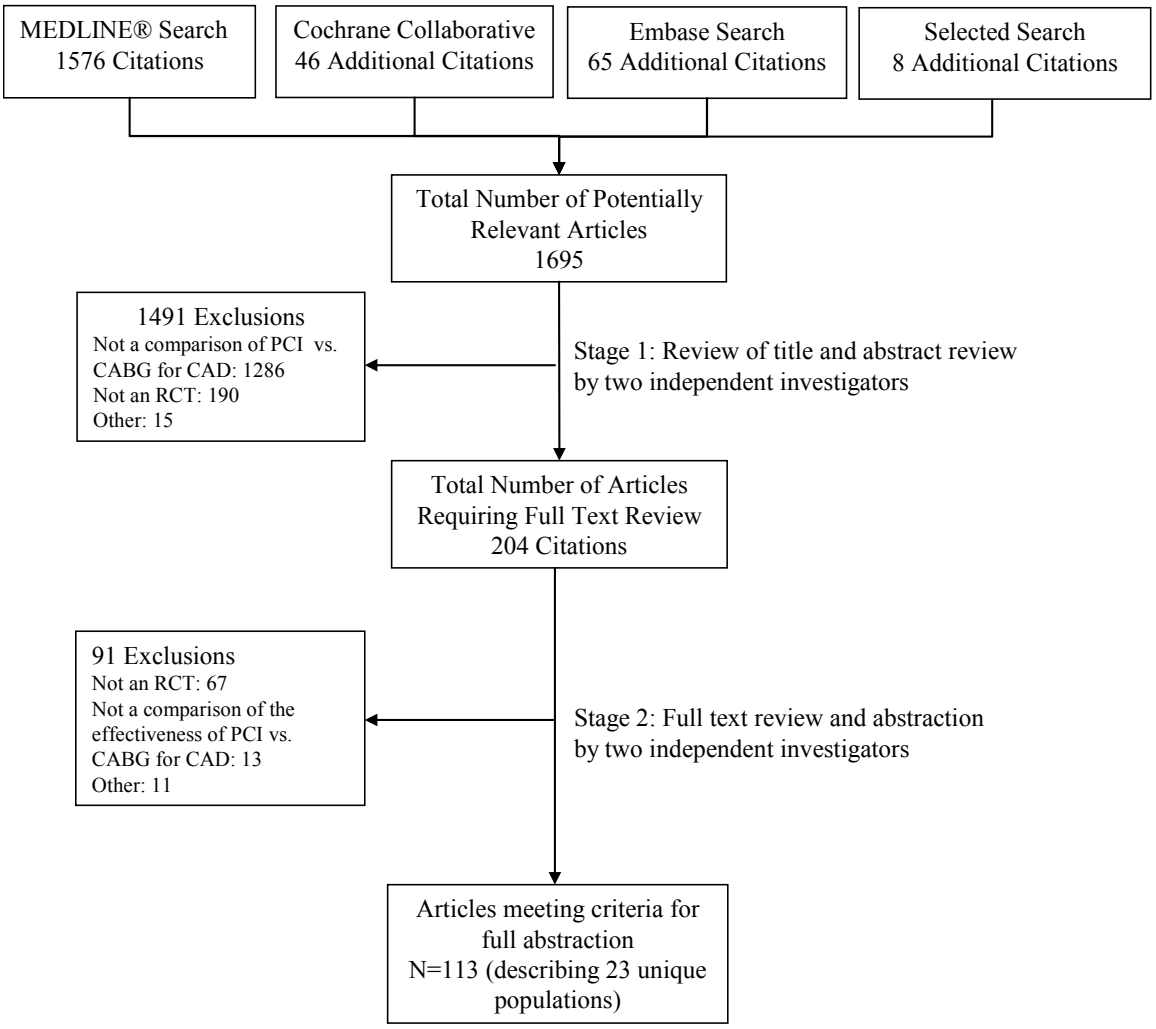
Peer Review and Public Commentary

A draft of this Evidence Report was reviewed by experts in coronary artery disease, PCI technologies, and CABG technologies (Appendix D). These experts were either directly invited by the EPC or offered comments through a public review process. Revisions of the draft were made, where appropriate, based on their comments. The draft and final reports were also reviewed by staff from the Scientific Resource Center at Oregon Health and Science University. However, the findings and conclusions are those of the authors, who are responsible for the contents of the report.

Results

Our searches for RCTs comparing the effectiveness of PCI and CABG yielded 1695 potentially relevant articles of which 204 articles merited full-text review (Figure 1). A total of 113 articles reporting on 23 unique populations met our inclusion criteria. Appendix B provides the citations of articles excluded after the full text review with the reason for exclusion.

Figure 1. Search results for RCTs



RCT=randomized controlled trial; PCI=percutaneous coronary intervention; CABG=coronary artery bypass grafting; CAD=coronary artery disease

Our searches for registries yielded 94 potentially relevant articles on ten registries that met our inclusion criteria. In the sections that follow, we first present an overview of the included RCTs and observational studies and then present the evidence relevant to each of the key questions.

General Description of Included Studies

Description of the Randomized Controlled Trials

We identified 23 RCTs that enrolled a total of 9,963 patients (5019 who received PCI and 4944 who received CABG) (Table 3). We also identified a collaborative pooling of patient data from four of the included RCTs.[17]

Trials were evenly split between single center and multi-center studies, and most were conducted in Europe or the United Kingdom, or both (only three trials were performed in the United States) (Table 4). Trials were conducted in two major waves: the early studies (patient entry 1987-1993) principally used balloon angioplasty as the PCI technique, and the recent studies (1994-2002) principally used stents as the PCI technique. Only one small trial of PCI versus CABG used drug-eluting stents.[34] Nine trials limited entry to patients with single-vessel disease of the proximal left anterior descending (LAD) artery, while the remaining 14 trials enrolled patients with multi-vessel disease, either exclusively (11 trials) or predominantly (three trials) (Table 5).

Trial participants averaged 61 years of age, and 27% were women (Appendix C Table 1). The vast majority of patients were of European ancestry, since most trials were conducted in Europe and only 5-7% of patients in the US-based studies were of African American ancestry (less than 2% of patients randomized in all trials). The baseline clinical characteristics of trial participants were typical for a population of patients with coronary disease: roughly 20% had diabetes, half had hypertension, and half had hyperlipidemia (Appendix C Table 2). While roughly 40% of patients had a prior myocardial infarction, the prevalence of heart failure was low, and left ventricular function was generally well preserved. Among studies that enrolled patients with multi-vessel coronary disease, most patients had two-vessel rather than three-vessel disease (Table 6).

Revascularization procedures were generally performed with standard methods for the time period of the trial (Appendix C Table 3). Among patients with multi-vessel disease, more grafts were placed during CABG than vessels dilated during PCI (Appendix C Table 3). Among PCI-assigned patients, use of stents and adjunctive therapy with aspirin, clopidogrel or ticlopidine, and heparin was common in the recent studies, but not in the earlier trials conducted when balloon angioplasty was standard. Arterial grafting with the left internal mammary artery (LIMA) was frequently employed, especially in more recent trials. A minority of CABG procedures were performed off-pump, although a few studies used minimally invasive direct coronary artery bypass (MIDCAB) incisions and beating heart operations to perform CABG in patients with single-vessel LAD disease (Appendix C Table 3).

Quality of the Randomized Controlled Trials

The quality of most trials was high and 21 trials received a grade of "A" because their randomization methods were sound and clearly explained, their dropout rates were low, and they performed intention-to-treat analyses. The Seoul-Kim[35] trial received a grade of "B" because it was not clear that there was concealment of allocation or intention-to-treat, and some data were obtained via a "retrospective review" of charts. The Seoul-Hong[34] trial received a grade of "C"

because it may not have been truly randomized, as the imbalance between the number of patients assigned to PCI (119) and to CABG (70) is unlikely to have arisen by chance. Neither the authors nor the journal editor responded to requests for clarification of the method of randomization. In addition, the trial from Seoul-Hong is small and has a very short follow-up (six months). We performed sensitivity analyses by removing this study from the analysis of our main outcomes to evaluate the effect of this trial's outcomes on our results. We note that the Seoul-Hong trial is the only included trial that compared PCI using drug-eluting stents with CABG.

Table 3. Brief overview of the randomized controlled trials

AMIST—Angioplasty versus Minimally Invasive Surgery Trial. A small UK trial of 100 patients with single-vessel proximal LAD disease conducted 1999-2001.
Reeves BC, Angelini GD, Bryan AJ, et al. A multi-centre randomised controlled trial of minimally invasive direct coronary bypass grafting versus percutaneous transluminal coronary angioplasty with stenting for proximal stenosis of the left anterior descending coronary artery. Health Technol Assess. 2004 Apr;8(16):1-43.
ARTS—Arterial Revascularization Therapies Study. A large European trial of 1205 patients with MVD that used bare metal stents. One of four trials that participated in the pooling project of stent trials.
Serruys PW, Unger F, Sousa JE, et al. Comparison of coronary-artery bypass surgery and stenting for the treatment of multivessel disease. N Engl J Med. 2001 Apr 12;344(15):1117-24.
AWESOME—Angina with Extremely Serious Operative Mortality Evaluation. A medium-sized American Department of Veterans Affairs trial in 454 patients with medically refractory angina, high procedural risk, and single or multi-vessel disease.
Morrison DA, Sethi G, Sacks J, et al. Percutaneous coronary intervention versus coronary artery bypass graft surgery for patients with medically refractory myocardial ischemia and risk factors for adverse outcomes with bypass: a multicenter, randomized trial. Investigators of the Department of Veterans Affairs Cooperative Study #385, the Angina With Extremely Serious Operative Mortality Evaluation (AWESOME). J Am Coll Cardiol. 2001 Jul;38(1):143-9.
BARI—Bypass Angioplasty Revascularization Investigation. Large American-Canadian trial of 1829 patients that used balloon angioplasty and reported extensively on outcomes in patient subgroups. Extended follow-up to ten years has been reported.
The Bypass Angioplasty Revascularization Investigation (BARI) Investigators. Comparison of coronary bypass surgery with angioplasty in patients with multivessel disease. N Engl J Med. 1996 Jul 25;335(4):217-25.
CABRI—Coronary Angioplasty versus Bypass Revascularization Investigation. Large European trial of 1054 patients with MVD that used balloon angioplasty and had limited follow-up.
CABRI Trial Participants. First-year results of CABRI (Coronary Angioplasty versus Bypass Revascularisation Investigation). Lancet. 1995 Nov 4;346(8984):1179-84.
EAST—Emory Angioplasty Surgery Trial. A medium-sized, single-center American trial of 392 patients with MVD that used balloon angioplasty and reported extended follow-up to eight years.
King SB, 3rd, Lembo NJ, Weintraub WS, et al. A randomized trial comparing coronary angioplasty with coronary bypass surgery. Emory Angioplasty versus Surgery Trial (EAST). N Engl J Med. 1994 Oct 20;331(16):1044-50.
ERACI-I—Argentine Randomized Trial of PTCA versus CABG in Multi-vessel Disease. A small Argentine trial of 127 patients with MVD that used balloon angioplasty and had limited follow-up.
Rodriguez A, Boullon F, Perez-Balino N, et al. Argentine randomized trial of percutaneous transluminal coronary angioplasty versus coronary artery bypass surgery in multivessel disease (ERACI): in-hospital results and 1-year follow-up. ERACI Group. J Am Coll Cardiol. 1993;22(4):1060-7.

Table 3. Brief overview of the randomized controlled trials (continued)

ERACI-II—Second Argentine Randomized Trial of PTCA versus CABG in Multi-vessel Disease.
A medium-sized trial of 450 patients with MVD conducted by the same Argentine group that organized ERACI-I. The trial used bare metal stents and was one of four trials that participated in the primary data pooling project

Rodriguez A, Bernardi V, Navia J, et al. Argentine Randomized Study: Coronary Angioplasty with Stenting versus Coronary Bypass Surgery in patients with Multiple-Vessel Disease (ERACI II): 30-day and one-year follow-up results. ERACI II Investigators. Journal of the American College of Cardiology. 2001 Jan;37(1):51-8.

GABI—German Angioplasty Bypass Surgery Investigation.
A medium-sized German trial of 359 patients with MVD that used balloon angioplasty and has reported the longest follow-up of any PCI-CABG trial (13 years).

Hamm CW, Reimers J, Ischinger T, et al. A randomized study of coronary angioplasty compared with bypass surgery in patients with symptomatic multivessel coronary disease. German Angioplasty Bypass Surgery Investigation (GABI). N Engl J Med. 1994 Oct 20;331(16):1037-43.

Groningen
A small, single-center Dutch study of 100 patients with single-vessel proximal LAD disease randomized to either stent implantation or minimally invasive bypass surgery.

Drenth DJ, Veeger NJGM, Winter JB, et al. A prospective randomized trial comparing stenting with off-pump coronary surgery for high-grade stenosis in the proximal left anterior descending coronary artery: three-year follow-up. J Am Coll Cardiol. 2002 Dec 4;40(11):1955-60.

Lausanne
A small, single-center Swiss trial (134 patients) with single-vessel proximal LAD disease that used balloon angioplasty.

Goy JJ, Eeckhout E, Burnand B, et al. Coronary angioplasty versus left internal mammary artery grafting for isolated proximal left anterior descending artery stenosis. Lancet. 1994;343(8911):1449-53.

Leipzig
A small, single-center German study of 220 patients with single-vessel proximal LAD disease that compared bare-metal stents with minimally invasive CABG.

Diegeler A, Thiele H, Falk V, et al. Comparison of stenting with minimally invasive bypass surgery for stenosis of the left anterior descending coronary artery. N Engl J Med. 2002 Aug 22;347(8):561-6.

MASS-I—Medicine, Angioplasty, or Surgery Study.
A small, single-center Brazilian trial that used three treatment options for patients with single-vessel proximal LAD disease (only outcomes in patients assigned to PCI or CABG were used in this report)

Hueb WA, Bellotti G, de Oliveira SA, et al. The Medicine, Angioplasty or Surgery Study (MASS): a prospective, randomized trial of medical therapy, balloon angioplasty or bypass surgery for single proximal left anterior descending artery stenoses. J Am Coll Cardiol. 1995;26(7):1600-5.

MASS-II—Second Medicine, Angioplasty, or Surgery Study.
A medium-sized Brazilian trial of 408 patients with MVD conducted by the same investigators as the MASS-I trial. This study used bare-metal stents and was one of four trials that contributed to the primary data pooling project for stent trials.

Hueb W, Soares PR, Gersh BJ, et al. The medicine, angioplasty, or surgery study (MASS-II): a randomized, controlled clinical trial of three therapeutic strategies for multivessel coronary artery disease: one-year results. J Am Coll Cardiol. 2004 May 19;43(10):1743-51.

Myoprotect I
A small, single-center German trial of 44 high risk patients with left main or left main equivalent disease randomized to PCI supported by retroinfusion of the anterior cardiac vein or to bypass surgery.

Pohl T, Giehrl W, Reichart B, et al. Retroinfusion-supported stenting in high-risk patients for percutaneous intervention and bypass surgery: results of the prospective randomized myoprotect I study. Catheter Cardiovasc Interv. 2004;62(3):323-30.

Table 3. Brief overview of the randomized controlled trials (continued)

Octostent A medium-sized Dutch trial of 280 patients with single- or MVD comparing coronary stents with off-pump bypass surgery Eefting F, Nathoe H, van Dijk D, et al. Randomized comparison between stenting and off-pump bypass surgery in patients referred for angioplasty. Circulation. 2003 Dec 9;108(23):2870-6.
Poland A small, single-center Polish trial of 100 patients with single-vessel proximal LAD disease comparing coronary stenting with minimally invasive direct coronary bypass grafting. Cisowski M, Drzewiecki J, Drzewiecka-Gerber A, et al. Primary stenting versus MIDCAB: preliminary report-comparision of two methods of revascularization in single left anterior descending coronary artery stenosis. Ann Thorac Surg. 2002;74(4):S1334-9.
RITA—Randomized Intervention Treatment of Angina. A large UK trial of 1011 patients with single-or MVD comparing balloon angioplasty with bypass surgery. Henderson RA, Pocock SJ, Sharp SJ, et al. Long-term results of RITA-1 trial: clinical and cost comparisons of coronary angioplasty and coronary-artery bypass grafting. Randomised Intervention Treatment of Angina. Lancet. 1998 Oct 31;352(9138):1419-25.
Seoul-Hong A small, single-center Korean trial of 189 patients with proximal LAD disease comparing treatment with DES to MIDCAB. Hong SJ, Lim D-S, Seo HS, et al. Percutaneous coronary intervention with drug-eluting stent implantation vs. minimally invasive direct coronary artery bypass (MIDCAB) in patients with left anterior descending coronary artery stenosis. Catheter Cardiovasc Interv. 2005 Jan;64(1):75-81.
Seoul-Kim A small, single-center Korean trial of 100 patients with proximal LAD disease comparing treatment with BMS to MIDCAB. Kim JW, Lim DS, Sun K, et al. Stenting or MIDCAB using ministernotomy for revascularization of proximal left anterior descending artery? Int J Cardiol. 2005 Mar 30;99(3):437-41.
SIMA—Stenting versus Internal Mammary Artery study. A small European trial of 123 patients with isolated proximal LAD disease comparing coronary stenting to MIDCAB. Goy JJ, Kaufmann U, Goy-Eggenberger D, et al. A prospective randomized trial comparing stenting to internal mammary artery grafting for proximal, isolated de novo left anterior coronary artery stenosis: The SIMA trial. Mayo Clin Proc. 2000;75(11):1116-23.
SoS—Stent or Surgery. A large European-Canadian trial of 988 patients with MVD comparing coronary stenting with CABG. One of four trials that contributed to the individual data pooling project for stent trials. SoS Investigators. Coronary artery bypass surgery versus percutaneous coronary intervention with stent implantation in patients with multivessel coronary artery disease (the Stent or Surgery trial): a randomised controlled trial. Lancet. 2002 Sep 28;360(9338):965-70.
Toulouse A small, single-center French study of 152 patients with single-vessel proximal LAD disease comparing balloon angioplasty with bypass surgery. Carrie D, Elbaz M, Puel J, et al. Five-year outcome after coronary angioplasty versus bypass surgery in multivessel coronary artery disease: results from the French Monocentric Study. Circulation. 1997;96(9 Suppl):II-1-6.

PCI=percutaneous coronary intervention; PTCA=percutaneous transluminal coronary intervention; CABG=coronary artery bypass grafting; MIDCAB=minimally-invasive coronary artery bypass grafting; BMS=bare-metal stent; DES=drug-eluting stent; MVD=multi-vessel disease; SVD=single-vessel disease; LAD=left anterior descending

Table 4. General description of the randomized controlled trials

Trial (Associated References)	Number of enrolling centers	Countries	Setting	Years of enrollment	Number of subjects randomized		PCI Intervention	Surgical Intervention
					PCI	Surgery		
AMIST[36]	6	UK	Cardiac centers: 100%	1999 to 2001	50	50	Stents available, not required	LIMA to LAD
ARTS[37] (38-49)	67	Canada; UK; Europe; South America	Cardiovascular centers: 100%	1997 to 1998	600	605	Bare metal stent	Standard CABG with at least one arterial conduit
AWESOME[50] (51-57)	16	US	Academic Centers: 94%; Community Hospitals: 6%	1995 to 2000	222	232	Operator choice of balloon angioplasty, stents, atherectomy, adjunctive pharmacologic support.	Surgeon choice of conduits, cardioplegia, sternotomy or thoracotomy, off-pump or on-pump.
BARI[58] (59-86)	18	US; Canada	Academic Centers: 100%	1988 to 1991	915	914	Balloon angioplasty	Standard CABG
CABRI[87] (88-93)	26	UK; Europe	Not specified	1988 to 1992	541	513	Balloon angioplasty	Standard CABG with arterial graft encouraged
EAST[94] (95-103)	1	US	Academic Centers: 100%	1987 to 1990	198	194	Balloon angioplasty; 40% staged procedures	Standard CABG.
ERACI-I [104] (105)	1	South America	Academic Centers: 100%	1988 to 1990	63	64	Balloon angioplasty	Hypothermic arrest, blood cardioplegia. LIMA used when possible.
ERACI-II[106] (107, 108)	7	South America	Not specified	1996 to 1998	225	225	Bare metal stent	Standard CABG. Arterial conduits encouraged.
GABI[109] (110, 111)	8	Europe	Academic Centers: 62.5%; Other: 37.5%	1986 to 1991	182	177	Balloon angioplasty	Standard CABG

Table 4. General description of the randomized controlled trials (continued)

Trial (Associated References)	Number of enrolling centers	Countries	Setting	Years of enrollment	Number of subjects randomized		PCI Intervention	Surgical Intervention
					PCI	Surgery		
Groningen[112] (113-115)	1	Europe	Academic Centers: 100%	1997 to 1999	51	51	Bare metal stent	LIMA using small left anterior thoracotomy, beating heart with mechanical stabilizer
Lausanne[116] (117)	1	Europe	Academic Centers: 100%	1989 to 1993	68	66	Balloon angioplasty	median sternotomy, LIMA, hypothermia
Leipzig[118] (119, 120)	1	Europe	Academic Centers: 100%	1997 to 2001	110	110	Bare metal stent	MIDCAB: limited left anterolateral thoractomy, LIMA with mechanical stabilizers, beating heart.
MASS[121] (122)	1	South America	Academic Centers: 100%	1988 to 1991	72	70	Balloon angioplasty	LIMA, mild hypothermia, extracorporeal circulation
MASS-II[123] (124, 125)	1	South America	Academic Centers: 100%	1995 to 2000	205	203	Operator choice BMS, lasers, atherectomy, balloon.	LIMA encouraged. Normothermic arrest with blood cardioplegia.
Myoprotect I[126]	1	Europe	Academic Centers: 100%	1998 to 2001	23	21	PCI with retroinfusion catheter in cardiac venous system	Standard CABG, off-pump by operator choice.
Octostent[127] (128, 129)	3	Europe	Academic Centers: 33%; Other: 67%	1998 to 2000	138	142	Bare metal stent	Off-pump CABG with Octopus tissue stabilizer. Operator choice of median sternotomy or left anterior thoracotomy. Arterial grafting encouraged.
Poland[130] (131)	1	Europe	Academic Centers: 100%	2000 to 2001	50	50	Bare metal stent	MIDCAB: LIMA under mechanical stabilization on beating heart through anterior thoracotomy.
RITA-1[132] (133-137)	16	UK	Not specified	1988 to 1991	510	501	Balloon angioplasty	Standard CABG.

Table 4. General description of the randomized controlled trials (continued)

Trial (Associated References)	Number of enrolling centers	Countries	Setting	Years of enrollment	Number of subjects randomized		PCI Intervention	Surgical Intervention
					PCI	Surgery		
Seoul-Hong[34]	1	Asia	Academic Centers: 100%	2003	119	70	Drug-coated stent	Off-pump LIMA with mechanical stabilization on beating heart, anterolateral thoractomy
Seoul-Kim[35]	1	Asia	Academic Centers: 100%	2000-2001	50	50	Bare metal stent	MIDCAB: LIMA with mechanical stabilization on beating heart through ministernotomy
SIMA[138]	6	Europe	Academic Centers: 50%; Community Hospitals: 50%	1994 to 1998	63	60	Bare metal stent	Minimally invasive, cardioplegia and hypothermia
SoS[139 (140-145)]	53	Canada; UK; Europe		1996 to 1999	488	500	Bare metal stent	Standard CABG, 93% use of IMA.
Toulouse[146]	1	Europe	Academic Centers: 100%	1989 to 1993	76	76	Balloon angioplasty	Standard CABG, 58% use of IMA.

PCI=percutaneous coronary intervention; CABG=coronary artery bypass grafting; UK=United Kingdom; US=United States; LIMA=left internal mammary artery; IMA=internal mammary artery; LAD=left anterior descending artery; MIDCAB=minimally invasive direct coronary artery bypass; BMS=bare metal stent

Table 5. Randomized controlled trials inclusion and exclusion criteria

Trial	Inclusion criteria						Exclusion criteria											
	MVD	SVD	PCI eligible lesion	Stable or unstable angina	Positive stress test	Other	Prior CABG	Prior PCI	Prior stroke or TIA	Age (years)	Left main CAD	SVD	Total occlusion	LVEF	Unsuitable coronary anatomy	Recent MI	Life limiting illness	Other HD
AMIST[36]		✓			✓		✓	✓					✓	<30%	✓			
ARTS[37]	✓		at least 2				✓	✓	✓		✓	✓		30%	✓	✓		
AWESOME[50]				✓		✓a		in last 6 months			✓						✓	✓
BARI[58]	✓						✓	✓		<80	✓	✓			✓		✓	
CABRI[87]	✓		1	✓		✓b	✓	✓	✓	<76	✓	✓		35%		✓	✓	✓
EAST[94]	✓						✓	✓			✓	✓	✓	25%	✓	✓		
ERACI-I[104]	✓		✓		✓						✓	✓		35%	✓	✓	✓	✓
ERACI-II[106]	✓				✓	✓c	✓	✓					✓	< 35%	✓	✓	✓	✓
GABI[109]	✓		at least 2				✓	✓		<75	✓	✓	✓		✓	✓		
Groningen[112]		✓					✓	✓	✓					✓		✓		
Lausanne[116]		✓			✓	✓d	✓	✓			✓			50%	✓	✓		
Leipzig[118]		✓				✓e	✓	✓					✓		✓			✓
MASS-I[121]		✓					✓	✓			✓			✓	✓			
MASS-II[123]	✓				✓		✓	✓			✓			<40%	✓	✓		✓

Table 5. Randomized controlled trials inclusion and exclusion criteria (continued)

Trial	Inclusion criteria						Exclusion criteria											
	MVD	SVD	PCI eligible lesion	Stable or unstable angina	Positive stress test	Other	Prior CABG	Prior PCI	Prior stroke or TIA	Age (years)	Left main CAD	SVD	Total occlusion	LVEF	Unsuitable coronary anatomy	Recent MI	Life limiting illness	Other HD
Myoprotect I[126]	✓		at least 1			✓f										✓	✓	
Octostent[127]	✓		at least 1	✓		✓g	✓	in last 6 months		> 18	✓		✓	✓	✓	✓	✓	
Poland[130]		✓				✓h	✓	✓					✓	40%		✓		✓
RITA-1[132]	✓			✓			✓	✓			✓						✓	✓
Seoul-Hong[34]		✓					✓	✓					✓			✓		
Seoul-Kim[35]		✓		✓		✓i	✓	✓			✓				✓			✓
SIMA[138]		✓												45%				
SoS[139]	✓		at least 1				✓	✓								✓	✓	
Toulouse[146]	✓						✓	✓		> 40	✓		✓		✓		✓	

MVD=multi-vessel disease; SVD=single-vessel disease (single-vessel or proximal Left Anterior Descending); PCI=percutaneous coronary intervention; CABG=coronary artery bypass graft; TIA=transient ischemic attack; CAD=Coronary Artery Disease; LVEF=Left ventricular ejection fraction; MI=myocardial infarction; HD=heart disease

a=Refractory ischemia; high risk for adverse outcomes (either over age 70, one or more prior open heart operations, LVEF < 0.35, MI within the last 7 days, or intraaortic balloon pump necessary to stabilize) b=At least 1 lesion (> 50% reduction in luminal diameter) and the vessel distal to the lesion at least 2 mm; c=A stress test that showed a large area or multiple areas of ischemia; At least one vessel to be stented had to have > 3mm diameter; LM was OK if interventionalist was comfortable stenting; d=documented ischemia by ETT or spontaneous ST changes with pain; e=minimum stenosis 75%; f=main-stem or a main-stem-equivalent lesion (defined as a leading proximal left anterior descending coronary artery (LAD) stenosis or stenosis of and LAD bypass (>/=75%) with concomitantly documented proximal occlusion of the right coronary artery and/or the left circumflex artery and a history of myocardial infarction); symptomatic coronary artery disease; Parsonnet score >6; g=Refractory ischemia; normal or moderately impaired global left ventricular function; one or more significant stenosis in at least one major epicardial coronary artery (LAD, left CX, RCD, or combo of one of the former and a side branch providing different myocardial territories); **Left circumflex--only patients in whom one graft needs to be inserted are eligible; h=CCS class II or higher angina; minimum stenosis 70% in LAD; minimum artery diameter 3 mm; minimum lesion length 20 mm; no significant lesions in other arteries; ARTS excluded patients with aspirin or ticlopidine allergies; Myoprotect 1 excluded patients with aspirin or clopidogrel allergies; Poland excluded patients with insulin dependent diabetes; i=minimum stenosis 70%

Table 6. Randomized controlled trials subjects' baseline coronary anatomy

Trial	Inter-vention	Mean Number diseased vessels	I VD %	2 VD %	3 VD %	LAD (prox)	LAD (other)	LAD (any)	LCX	RCA
AMIST[36]	PCI		100*			100**				
	CABG		100*			100**				
ARTS[37]	PCI	2.8	2	68	30			90	71	71
	CABG	2.8	0	67	33			90	72	72
AWESOME[50]	PCI		20	40	40			87		
	CABG		17	33	50			88		
BARI[58]	PCI		2	57	41	36				
	CABG		2	58	41	37				
CABRI[87]	PCI	2.4	2	58	40					
	CABG	2.4	1	56	43					
EAST[94]	PCI	3.4		60	40	71				
	CABG	3.4		60	40	74				
ERACI-I[104]	PCI			57	43			38	33	29
	CABG			53	47			37	30	34
ERACI-II[106]	PCI			40	55	50		91		
	CABG			38	58	52		93		
GABI[109]	PCI			85	15					
	CABG			78	22					
Groningen[112]	PCI		100*			100				
	CABG		100*			100				
Lausanne[116]	PCI		100			100				
	CABG		100			100				
Leipzig[118]	PCI		100*			100**				
	CABG		100*			100**				
MASS-I[121]	PCI		100			100				
	CABG		100			100				
MASS-II[123]	PCI			42	58			93		
	CABG			42	58			93		
Myoprotect I[126]	PCI	2.7		17	65		30	52		
	CABG	2.6		33	81		19	43		
Octostent[127]	PCI		68	30	1			88	17	27
	CABG		74	24	2			90	18	20
Poland[130]	PCI		100*			100**				
	CABG		100*			100**				
RITA-1[132]	PCI	1.7	46	42	12					
	CABG	1.7	44	43	12					
Seoul-Hong[34]	PCI		100*			100				
	CABG		100*			100				
Seoul-Kim[35]	PCI		100*			100**				
	CABG		100*			100**				
SIMA[138]	PCI		100*			100**				
	CABG		100*			100**				
SoS[139]	PCI			63	37	48	44		70	74
	CABG			52	47	44	48		75	79

Table 6. Randomized controlled trials subjects' baseline coronary anatomy (continued)

Trial	Inter-vention	Mean Number diseased vessels	I VD %	2 VD %	3 VD %	LAD (prox)	LAD (other)	LAD (any)	LCX	RCA
Toulouse[146]	PCI			72	28			91	71	54
	CABG			70	30			89	70	59

*This study included patients with single-vessel disease (SVD) only; however, the final percentage of group with SVD was not specified.
**Study design included patients with proximal LAD disease only; however, the final percentage of patients with proximal LAD disease was not reported. Poland did not report data on diseased vessels. VD=diseased vessels; LAD (prox)=proximal left anterior descending artery; LCX=left circumflex artery; RCA=right circumflex artery

Description of Observational Studies

Our searches identified 357 potentially relevant observational studies: 104 articles from the Scientific Resource Center MEDLINE® search, 161 articles from our MEDLINE® search, 85 articles from expert consultants, and seven from our initial RCT search. Twenty-eight of these related to the generalizability of RCT data and 68 and nine related to key questions 2g and 2h, respectively—the key questions for which insufficient RCT data were available. Key registries identified during the searches are described briefly in Table 7 and are mapped to the key questions for which their results supplemented RCT data. The references presented in Table 7 encompass all articles identified for Key Questions 1a and 2h; additional articles identified for Key Question 2g are presented in Appendix C Tables 8-13. We show comparisons of the RCT and observational studies populations in Table 8 and Figure 2 and describe the salient differences between them in the sections that follow. Details about the results for each key question are presented in the corresponding sections of the report.

Quality of Observational Studies

Overall the quality of the observational studies was high and each received an "A" grade on the basis of enrolling large numbers of subjects who had good follow-up and adequate descriptions of most key subject characteristics.

Table 7. Overview of selected registries

Registry Name	Description	References from the Registry Addressing Key Questions		
		KQ 1	KQ 2g	KQ 2h
Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH)	A Multicenter clinical registry of all cardiac catheterization procedures in the Canadian province of Alberta, in the period 1995-1998.	[147]		
American College of Cardiology National Cardiovascular Disease Registry (ACC)	Multicenter voluntary registry of coronary angioplasty procedures.		[148-150]	

Table 7. Overview of selected registries (continued)

Registry Name	Description	References from the Registry Addressing Key Questions		
		KQ 1	KQ 2g	KQ 2h
Angina with Extremely Serious Operative Mortality Evaluation (AWESOME) Registry	A Multicenter clinical registry of patients eligible for the AWESOME trial but not randomized	151		52
Bypass Angioplasty Revascularization Investigation (BARI) Registry	A Multicenter registry established in parallel with a randomized clinical trial. Includes patients who were eligible but not randomized, and a sample of patients who were clinically eligible but angiographically excluded.	152		
Cleveland Clinic	A single institution clinical registry of all coronary revascularization procedures at a major referral hospital. Reports cover procedures performed 1992-2000.	153		154, 155
Duke	A single institution clinical registry of all procedures at a major referral center. Reports cover procedures 1984-2000.	156-159		
Emory	A single institution registry of PCI and CABG procedures, 1980-1994.	160, 161		162-166
Emory Angioplasty Surgery Trial (EAST) Registry	A single center clinical registry of patients eligible for the EAST trial but not randomized.	167		
Hospital Corporation of America (HCA)	A multicenter administrative database from a system of 76 hospitals in 17 states performing PCI or CABG 1999-2002.	168		
Kansas City (Mid-American Heart Institute)	A single center clinical registry of patients undergoing PCI and CABG 1987-1989			169
Mayo Clinic	A single-center institution registry of all PCI and CABG procedures, 1982-1991	170		
Medicare	A multicenter administrative database from a publicly-funded health insurance program for those 65 and older administered by the US government.	171-176	177-185	
New York State Registry (NYSR)	A state mandated clinical registry collecting data from all hospitals in New York State.	186-188	189-200	
Northern New England	A Multicenter clinical registry of all five centers in Maine, New Hampshire and Vermont performing coronary revascularization. Reports on the period 1992-1996.	201-203	204, 205	
Scottish Registry	Multicenter clinical registry of all CABG and PCI procedures in Scotland 1997-2003	206	207	
Society of Thoracic Surgeons (STS)	Multicenter voluntary registry of cardiac surgery, with procedural data and outcomes from up to 500 sites.	208, 209	210, 211	
Multi-state Registries	NYSR/State of California—Contains data from the NYSR and State of California obtained through Patient Discharge Database of the Office of Statewide Health Planning and Development		212	

This table presents selected registries used to analyze both the generalizability of the RCT data and address Key Questions left unanswered by the RCTs. Observational studies describing these registries were found through a variety of literature sources, including: MEDLINE® searches, Scientific Resource Center supplemental searches, expert input, and web searches. In each of the sections describing the Key Questions, we describe more fully the particular observational studies pertinent to that section. PCI=percutaneous coronary intervention; CABG=coronary artery bypass grafting

Table 8. Comparison of randomized controlled trials and registry populations

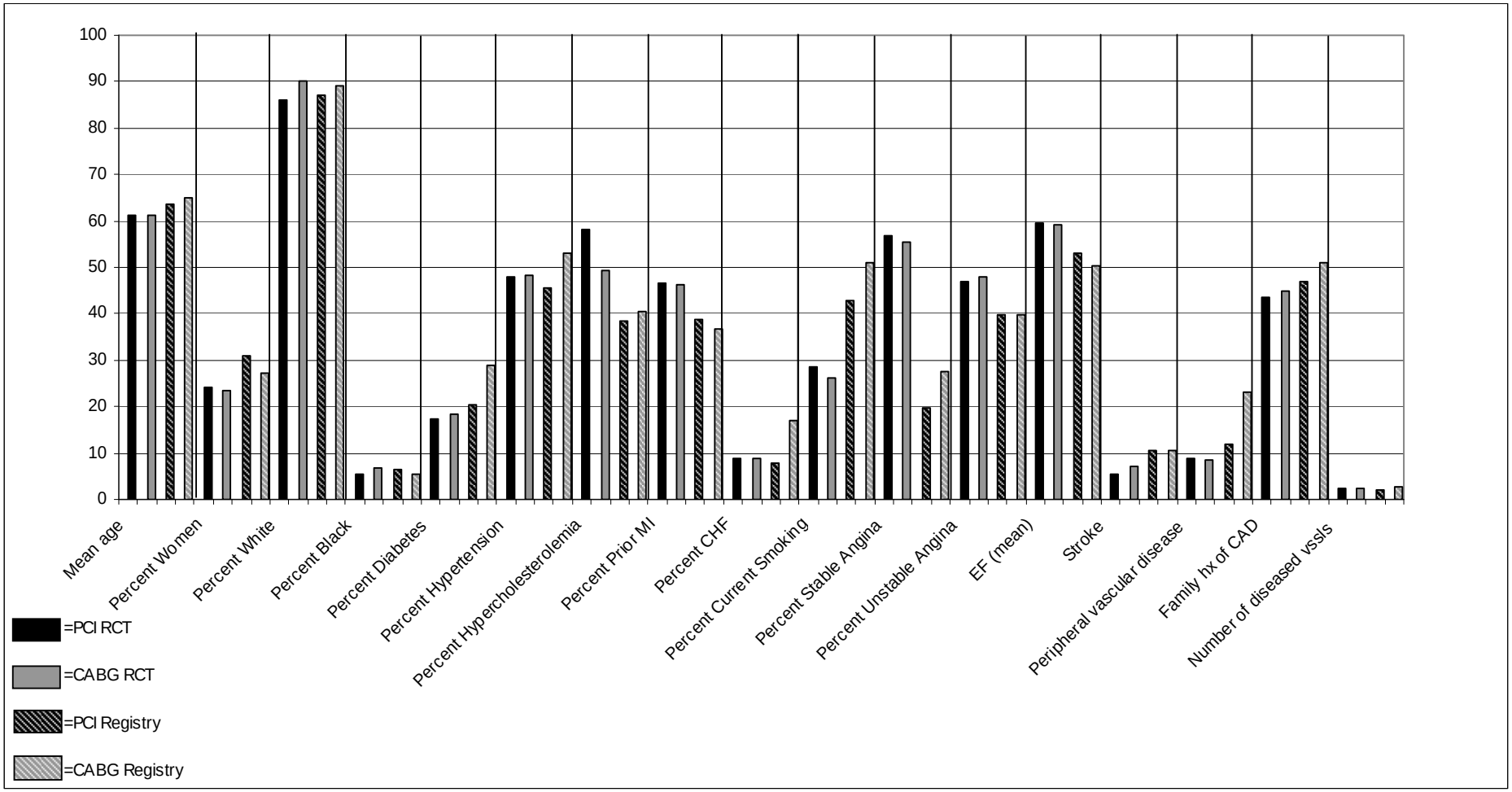
Characteristic	Type of Study	Number of trials/studies	Weighted Mean	Weighted Median
Age (Median)	PCI/RCT	20	61.3	61.0
	PCI/Registry	11	63.5	65
	CABG/RCT	21	61.2	61.1
	CABG/Registry	13	65.0	67.0
Women (%)	PCI/RCT	21	24.3	23.0
	PCI/Registry	11	31.0	31.4
	CABG/RCT	21	23.4	22.0
	CABG/Registry	12	27.2	28.6
White (%)	PCI/RCT	4	86.1	91.0
	PCI/Registry	2	87.0	87.0
	CABG/RCT	3	90.2	89.0
	CABG/Registry	2	89.1	89.0
African-American (%)	PCI/RCT	2	5.4	5.0
	PCI/Registry	2	6.4	6.4
	CABG/RCT	2	6.8	7.0
	CABG/Registry	2	5.4	5.5
Diabetes (%)	PCI/RCT	11	17.4	19.0
	PCI/Registry	12	20.3	17.4
	CABG/RCT	11	18.4	17.0
	CABG/Registry	14	29.0	33.0
HTN (%)	PCI/RCT	10	47.9	46.0
	PCI/Registry	9	45.6	46.0
	CABG/RCT	10	48.3	49.0
	CABG/Registry	11	53.2	53.0
Hyper-cholesterolemia (%)	PCI/RCT	7	58.2	58.0
	PCI/Registry	2	38.5	47.0
	CABG/RCT	7	49.4	58.0
	CABG/Registry	2	40.4	48.0
Prior MI (%)	PCI/RCT	9	46.6	44.0
	PCI/Registry	10	38.8	27.0
	CABG/RCT	9	46.1	42.0
	CABG/Registry	12	36.6	25.0
CHF (%)	PCI/RCT	1	9.0	9.0
	PCI/Registry	11	7.8	5.3
	CABG/RCT	1	9.0	9.0
	CABG/Registry	12	16.9	16.0
Current Smoking (%)	PCI/RCT	7	28.6	28.0
	PCI/Registry	6	42.8	25.0
	CABG/RCT	7	26.1	26.0
	CABG/Registry	6	50.9	65.0
Stable Angina (%)	PCI/RCT	7	56.7	57.0
	PCI/Registry	3	19.7	22.0
	CABG/RCT	7	55.6	60.0
	CABG/Registry	3	27.5	34.0
Unstable Angina (%)	PCI/RCT	9	47.0	37.0
	PCI/Registry	4	39.7	33.0

Table 8. Comparison of randomized controlled trials and registry populations (continued)

Characteristic	Type of Study	Number of trials/studies	Weighted Mean	Weighted Median
	CABG/RCT	9	48.0	35.0
	CABG/Registry	4	39.9	40.0
EF (Mean)	PCI/RCT	13	59.4	59.0
	CABG/RCT	13	59.2	60.0
	PCI/Registry	6	53.1	53.0
	CABG/Registry	9	50.4	50.0
Prior Stroke (%)	PCI/RCT	3	5.6	5.0
	PCI/Registry	2	10.5	11.0
	CABG/RCT	3	7.1	2.0
	CABG/Registry	2	10.5	11.0
PVD (%)	PCI/RCT	6	8.8	8.0
	PCI/Registry	3	11.8	11.0
	CABG/RCT	6	8.5	8.0
	CABG/Registry	3	23.0	18.0
Family history of CAD (%)	PCI/RCT	3	43.4	39.0
	PCI/Registry	1	47.0	47.0
	CABG/RCT	3	44.9	42.0
	CABG/Registry	1	51.0	51.0
Number Diseased Vessels (Mean)	PCI/RCT	7	2.3	2.4
	PCI/Registry	6	2.1	2.2
	CABG/RCT	7	2.3	2.4
	CABG/Registry	8	2.6	2.7

PCI=percutaneous coronary intervention; CABG=coronary artery bypass grafting; RCT=randomized controlled trials; HTN=hypertension; MI=myocardial infarction; CHF=congestive heart failure; EF=ejection fraction; PVD=peripheral vascular disease; CAD=coronary artery disease

Figure 2. Comparison of randomized controlled trials and registry populations



RCT=randomized controlled trials; MI=myocardial infarction; CHF=congestive heart failure; EF=ejection fraction; CAD=coronary artery disease

Key Question 1a. In patients with ischemic heart disease, and angiographically-proven single or multi-vessel disease, what is the comparative effectiveness of PCI compared to CABG, in reducing the occurrence of adverse objective outcomes and improving subjective outcomes?

For consistency, we adopted the following conventions for presenting the results: we present the summary risk difference as a percent difference, all outcomes were calculated in their "positive frame" (e.g., survival rather than mortality, freedom from angina rather than angina, etc.), and all of the forest plots are oriented such that the studies on the left of the origin favor CABG and those to the right of the origin favor PCI. We present PCI-CABG risk differences such that positive numbers favor PCI and negative numbers favor CABG. Similarly, PCI/CABG odds ratios greater than 1.0 favor PCI and ratios less than 1.0 favor CABG.

Short-Term/Procedural Outcomes

Short-term, procedural complications were typically more common among CABG-assigned patients than PCI-assigned patients in the randomized trials (Appendix C Table 4); however, these differences did not generally reach statistical significance.[b]

Procedural survival

Short-term survival in randomized trials was relatively high for both procedures: only 59 of the 5019 PCI recipients died and only 85 of the 4944 CABG recipients died. When data from all randomized trials were combined, procedural survival did not differ significantly between procedures: PCI-CABG procedural survival difference was 0.1 percent (CI: -0.3 percent to +0.6 percent) and PCI/CABG odds ratio (OR) 1.4 (CI: 0.98 to 1.97) (Figure 3 and Appendix C Figure 1).

While procedural survival was not specifically reported by the SoS trial, we extracted it from the Kaplan Meier curve. Also, two trials, AWESOME and Myoprotect I had significantly worse short- and long-term outcomes than the other trials (Figure 4), likely because these trials enrolled patients who were more acutely ill. We recalculated the procedural survival excluding AWESOME and Myoprotect; the difference in procedural survival remained small (PCI-CABG procedural survival difference: 0.4 percent [CI: -0.1 percent to +0.8 percent]; PCI/CABG odds ratio: 1.4 [CI: 0.96 to 2.08]).

We also examined procedural survival according to whether the trial (1) enrolled single- or multi-vessel disease patients and (2) used balloon angioplasty or stents (Figures 5 and 6). We found no statistically significant differences between PCI and CABG recipients compared across these parameters. Similarly, we found no statistically significant differences between PCI and CABG when we examined the procedural survival according to whether the trial used the more

[b] In this section, we present the short-term/procedural outcomes which were reported either as "in-hospital," "procedural," or "within 30-days" of the procedure (if both "within 30-days" and "in-hospital" data were reported only "in-hospital" data were used in this analysis).

invasive on-pump/median sternotomy approaches versus MIDCAB/off-pump techniques (Appendix C Figure 2).

The procedural survival in PCI-CABG RCTs was higher than that reported by large clinical registries and administrative databases, even after taking into account the secular trends towards lower procedural risk over time for both CABG and PCI. For example, analyses from the Society of Thoracic Surgeons (STS) database has found that unadjusted operative survival rose from about 96.8 percent to 97.8 percent between 1996 and 2005, despite higher risk profiles among CABG patients (Table 9).[208] A detailed report of procedural survival in the STS database by Ferguson et al. found that operative survival rose from 96.1 percent in 1990 to 97.0 percent in 1999.[209] A study of CABG and PCI procedural outcomes from the Hospital Corporation of America from 1999 to 2002 found that, for the entire period, PCI survival was 98.75 percent vs. 97.37 percent for CABG and that survival for both procedures rose over time.[168] To evaluate whether the difference in procedural survival has changed over the past decade in randomized trials, we calculated the procedural survival difference according to the final year of subject recruitment (Figure 7). This analysis supports the conclusions of the large observational studies: namely, that the procedural survival of both procedures has increased over time and that the procedural survival after PCI is higher, albeit not statistically significantly so.

We identified six articles that compared short-term procedural outcomes of CABG and PCI among the US Medicare population (Table 9). The minimum age of patients included in these studies was 65 years which is approximately four years older than the average age of patients in the RCTs, and most were conducted in the 1980's. Procedural survival in the unselected Medicare population was substantially lower than in the randomized trials both for PCI and for CABG. The procedural survival of CABG patients was consistently lower than for PCI patients.

Other procedural outcomes

Freedom from procedural stroke was reported by 16 trials, and the freedom from stroke was significantly lower after CABG than after PCI (98.8 percent vs. 99.5 percent) (Figure 8). The PCI-CABG difference in freedom from procedural stroke of 0.6 percent (CI: +0.2 percent to +1 percent, p=0.002) and PCI/CABG odds ratio 1.96 (CI: 1.16 to 3.3, p=0.01) (Appendix C Figure 3) were statistically homogeneous.

We found that the definition of procedural myocardial infarction varied among studies and that post-procedure serial monitoring of electrocardiograms and serum biomarker levels was not routine, so that ascertainment of procedural myocardial infarctions may not have been complete. Freedom from procedural myocardial infarctions was somewhat heterogeneous among the trials (heterogeneity statistics for the PCI-CABG difference in freedom from procedural MI: Q-value 35.7, p value 0.01; I^2 46.8). However, when we performed sensitivity analyses, removing one study at a time, the overall results did not change. Freedom from procedural myocardial infarction was slightly higher among PCI recipients but was not statistically significant: PCI-CABG difference in freedom from procedural MI 0.1 percent (CI: -1.0 percent to +1.2 percent) (Figure 9) and PCI/CABG odds ratio 1.04 (CI: 0.71 to 1.5) (Appendix C Figure 4).

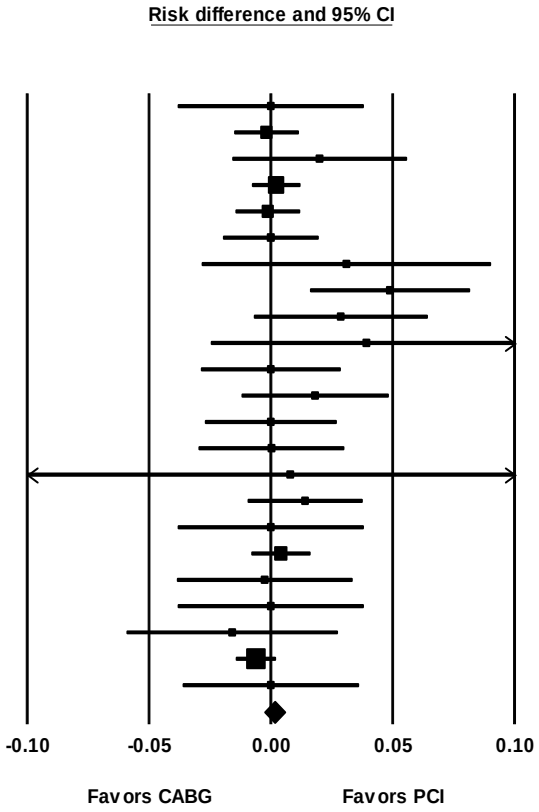
Other procedural outcomes were not generally reported or consistently defined by clinical trials, making it difficult to compare quantitatively the risk of non-fatal procedural adverse events such as pulmonary complications, renal failure, infections, heart failure, and arrhythmias.

Quality of evidence for procedural outcomes

We rated the quality of the evidence providing short term-procedural data as *acceptable* for mortality and stroke given that it comes from RCTs that were consistent and did not appear to be significantly affected by publication bias (Appendix C Figure 5). Event rates were low, however, which reduces the strength of inference, especially for mortality. The quality of the evidence regarding short term-procedural data for MI was *weak*, however. Although 19 RCTs of high quality reported procedural MI data, the results and the definitions of procedural MI were significantly heterogeneous.

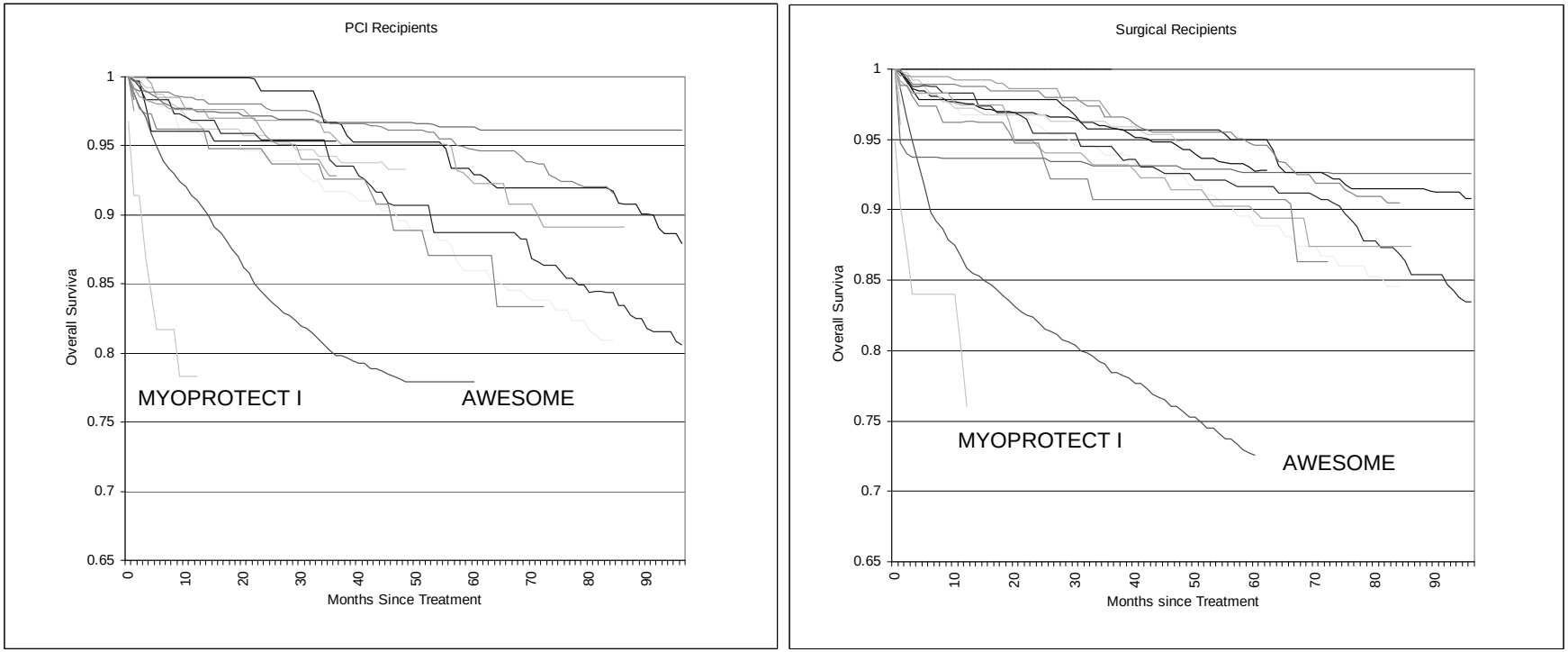
Figure 3. Procedural survival

Study name	Risk difference	Lower limit	Upper limit	p-Value	Survival / Total PCI	Survival / Total CABG
AMIST	0.000	-0.038	0.038	1.000	50 / 50	50 / 50
ARTS	-0.002	-0.015	0.012	0.794	591 / 600	597 / 605
AWESOME	0.020	-0.016	0.056	0.275	215 / 222	220 / 232
BARI	0.002	-0.008	0.012	0.666	905 / 915	902 / 914
CABRI	-0.001	-0.015	0.012	0.855	534 / 541	507 / 513
EAST	0.000	-0.020	0.020	1.000	196 / 198	192 / 194
ERACI	0.031	-0.028	0.090	0.307	62 / 63	61 / 64
ERACI II	0.049	0.016	0.082	0.004	223 / 225	212 / 225
GABI	0.029	-0.007	0.064	0.116	179 / 182	169 / 177
Groningen	0.039	-0.025	0.103	0.229	51 / 51	49 / 51
Lausanne	0.000	-0.029	0.029	1.000	68 / 68	66 / 66
Leipzig	0.018	-0.012	0.048	0.239	110 / 110	108 / 110
MASS	0.000	-0.027	0.027	1.000	72 / 72	70 / 70
MASS-II	0.000	-0.030	0.030	0.987	200 / 205	198 / 203
Myoprotect	0.008	-0.162	0.178	0.927	21 / 23	19 / 21
Octostent	0.014	-0.010	0.038	0.244	138 / 138	140 / 142
Poland	0.000	-0.038	0.038	1.000	50 / 50	50 / 50
RITA	0.004	-0.008	0.016	0.507	506 / 510	495 / 501
Seoul-Hong	-0.003	-0.039	0.034	0.891	117 / 119	69 / 70
Seoul-Kim	0.000	-0.038	0.038	1.000	50 / 50	50 / 50
SIMA	-0.016	-0.059	0.028	0.474	62 / 63	60 / 60
SoS*	-0.006	-0.014	0.002	0.150	484 / 488	499 / 500
Toulouse	0.000	-0.036	0.036	1.000	75 / 76	75 / 76
	0.001	-0.003	0.006	0.511	4960 / 5019	4859 / 4944



Heterogeneity Statistics: Q-value 20.3, P-value 0.6; I-squared 0.000.
PCI=percutaneous coronary intervention; CABG=coronary artery bypass grafting; CI=Confidence Interval

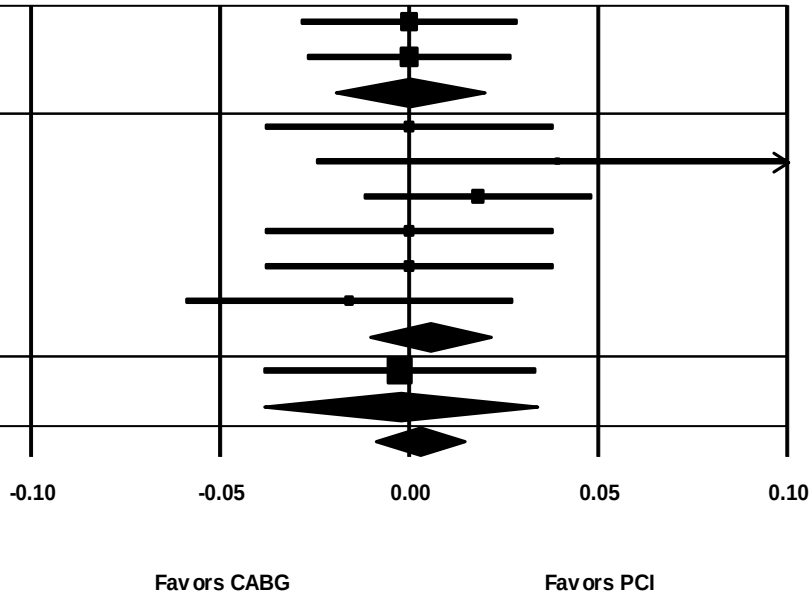
Figure 4. Survival (all studies by procedure)



PCI=percutaneous coronary intervention; CABG=coronary artery bypass grafting

Figure 5. Comparison of procedural survival in balloon angioplasty or stent trials versus CABG in patients with SVD

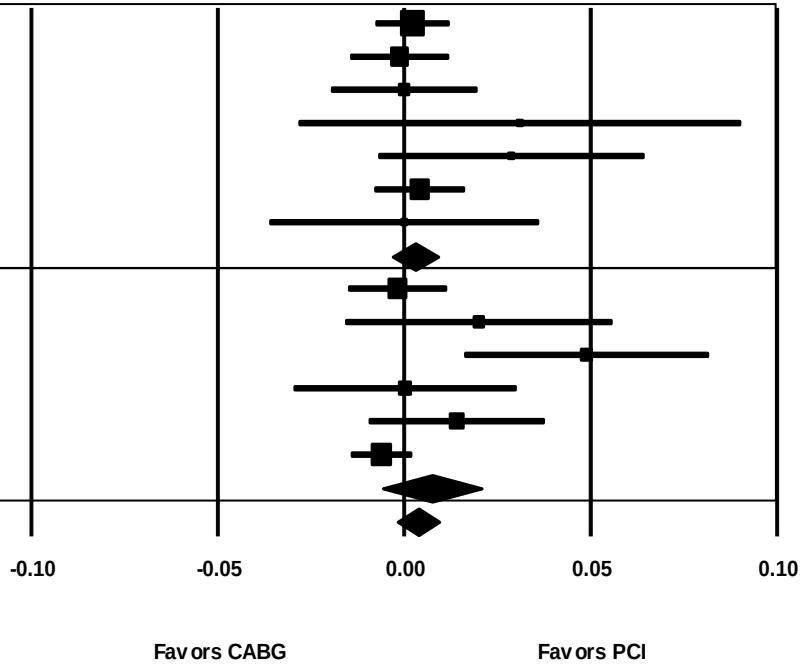
Study name	Statistics for each study				Survival / Total	
	Risk difference	Lower limit	Upper limit	p-Value	PCI	CABG
Lausanne	0.000	-0.029	0.029	1.000	68 / 68	66 / 66
MASS	0.000	-0.027	0.027	1.000	72 / 72	70 / 70
Summary for Balloon Trials	0.000	-0.020	0.020	1.000	140 / 140	136 / 136
AMIST	0.000	-0.038	0.038	1.000	50 / 50	50 / 50
Groningen	0.039	-0.025	0.103	0.229	51 / 51	49 / 51
Leipzig	0.018	-0.012	0.048	0.239	110 / 110	108 / 110
Poland	0.000	-0.038	0.038	1.000	50 / 50	50 / 50
Seoul-Kim	0.000	-0.038	0.038	1.000	50 / 50	50 / 50
SIMA	-0.016	-0.059	0.028	0.474	62 / 63	60 / 60
Summary for BMS Trials	0.005	-0.011	0.021	0.511	373 / 374	367 / 371
Seoul-Hong	-0.003	-0.039	0.034	0.891	117 / 119	69 / 70
Summary for DES Trials	-0.003	-0.039	0.034	0.891	117 / 119	69 / 70
Summary for All SVD Trials	0.003	-0.009	0.014	0.661	630 / 633	572 / 577



Balloon Trials: Heterogeneity Statistics: Q-value 0.0, P-value 1.0; I-squared 0.000. PCI/CABG Odds Ratio Analysis: Could not be performed since both survival differences are 0. BMS (Bare Metal Stent) Trials: Heterogeneity Statistics: Q-value 2.8, P-value 0.58; I-squared 0.000. PCI/CABG Odds Ratio Analysis: 2.22 (CI: 0.37, 13.37); p=0.4. DES (Drug Eluting Stent) Trials: Heterogeneity Statistics: Q-value 0, P-value 1; I-squared 0.000. PCI/CABG Odds Ratio Analysis: Could not be performed since survival difference is PCI=percutaneous coronary intervention; CABG=coronary artery bypass grafting; SVD=single-vessel disease; CI=Confidence Interval

Figure 6. Comparison of procedural survival in balloon angioplasty or stent trials versus CABG in patients with MVD

Study name	Statistics for each study				Survival / Total	
	Risk difference	Lower limit	Upper limit	p-Value	PCI	CABG
BARI	0.002	-0.008	0.012	0.666	905 / 915	902 / 914
CABRI	-0.001	-0.015	0.012	0.855	534 / 541	507 / 513
EAST	0.000	-0.020	0.020	1.000	196 / 198	192 / 194
ERACI	0.031	-0.028	0.090	0.307	62 / 63	61 / 64
GABI	0.029	-0.007	0.064	0.116	179 / 182	169 / 177
RITA	0.004	-0.008	0.016	0.507	506 / 510	495 / 501
Toulouse	0.000	-0.036	0.036	1.000	75 / 76	75 / 76
Summary for Balloon Trials	0.003	-0.003	0.009	0.376	2457 / 2485	2401 / 2439
ARTS	-0.002	-0.015	0.012	0.794	591 / 600	597 / 605
AWESOME	0.020	-0.016	0.056	0.275	215 / 222	220 / 232
ERACI II	0.049	0.016	0.082	0.004	223 / 225	212 / 225
MASS-II	0.000	-0.030	0.030	0.987	200 / 205	198 / 203
Octostent	0.014	-0.010	0.038	0.244	138 / 138	140 / 142
SoS*	-0.006	-0.014	0.002	0.150	484 / 488	499 / 500
Summary for BMS Trials	0.007	-0.006	0.020	0.283	1852 / 1878	1867 / 1907
Summary for All SVD Trials	0.004	-0.002	0.009	0.210	4309 / 4363	4268 / 4346



Balloon Trials: Heterogeneity Statistics: Q-value 3.4, P-value 0.8; I-squared 0.000. PCI/CABG Odds Ratio: 1.36; CI: 0.82, 2.25; p=0.2.
BMS (Bare Metal Stent) Trials: Heterogeneity Statistics: Q-value 13.2, P-value 0.02; I-squared 62.0. PCI/CABG Odds Ratio:1.46; CI: 0.68, 3.15; p=0.3.
Trial names followed by an asterisk indicate that the survival data were abstracted from Kaplan-Meier curves. PCI=percutaneous coronary intervention; CABG=coronary artery bypass grafting; MVD=multi-vessel disease; CI=Confidence Interval

Table 9. Procedural survival reported in observational studies

Study Reference	Registry	Population	Inter-vention	Number of Patients	Demographics					Unadjusted Procedural Survival %
					Mean Age	Women %	White %	Diabetes %	Prior MI %	
Feit et al.[152]	BARI	Patients in the registry arm of the BARI trial who underwent PCI or CABG	PCI	1189	61.0	26	94	15	50	99.3
			CABG	625	62.5	26	96	19	50	98.2
Brenner et al.[153]	Cleveland	Patients with MVD who underwent PCI or CABG 1995-1999	PCI	872	65	32		30	48	98.7
			CABG	5161	64	27		40	58	98.9
King et al.[167]	EAST registry	Patients in the registry arm of the EAST trial who underwent PCI or CABG	PCI	168						99.4
			CABG	270						98.9
Weintraub et al.[160]	Emory	Patients who underwent CABG 1973-1979	CABG	3939	54.5	18.9		12.5	54.1	99.0
Weintraub et al.[161]	Emory	Patients with 2VD who underwent PCI or CABG 1984-1985	PCI	415	57	18		10	44	100.0
			CABG	454	60	20		15	55	98.9
Mack et al.[168]	Hospital Corporation of America (HCA)	Patients undergoing either PCI or CABG	PCI 1999	26,868	65.6	35		25.6	45.6	98.6
			PCI 2002	32,060						98.8
			On-pump CABG 1999	12,786						97.1
			On-pump CABG 2002	11,418						97.8
			Off-pump CABG 1999	3024	66.5	29		33.3	40.4	97.6
			Off-pump CABG 2002	3474						97.6

Table 9. Procedural survival reported in observational studies (continued)

Study Reference	Registry	Population	Inter-vention	Number of Patients	Demographics					Unadjusted Procedural Survival %
					Mean Age	Women %	White %	Diabetes %	Prior MI %	
Harris et al.[170]	Mayo	Patients who underwent PCI or CABG 1982-1991	PCI 1/1982-4/1985	636	58	25		8	44	97.0
			PCI 5/1985-8/1988	1804	62	26		14	45	98.0
			PCI 9/1988-12/1991	2497	65	29		18	51	96.0
			CABG 1/1982-4/1985	2250	61.6	19.4			57.0	96.3
			CABG 5/1985-8/1988	2705	64.4	22.4			55.6	96.3
			CABG 9/1988-12/1991	2144	65.8	24.3			50.7	96.7
Rosen et al.[171], Geraci et al.[172], and Rosen et al.[173]	Medicare	Random sample of patients admitted 1/1985-6/1986 in Alabama, Arizona, Indiana, New York, Pennsylvania, Utah, and Wisconsin	PCI	693	70.4	37.5	97	15.6	31	96.5
			CABG	2213	70.7	29.6	97.6	19.8	44	93.4
Peterson et al.[174]	Medicare	Patients aged 65 years or older who had angioplasty or bypass surgery from 1987-1990	PCI	225,915	71.7	42.6	94.8			96.7
			CABG	357,885	71.6	33	95.2			94.2
Hartz et al.[175]	Medicare	Patients aged 65 years or older who had angioplasty or bypass surgery in 1985	PCI	25,423	68.7	38.4				96.2
			CABG	71,243	69.4	31.2				93.6
Venkatappa et al.[176]	Medicare	Patients who had a CABG 7/1995-6/996 and patients who had a CABG surgery from 7/1998 through 12/1998	CABG in 1995-1996	2312	70.8	33.7	94.5	27		96.4
			CABG 1998	926	71.6	35.2	93.4	31.9		95.1

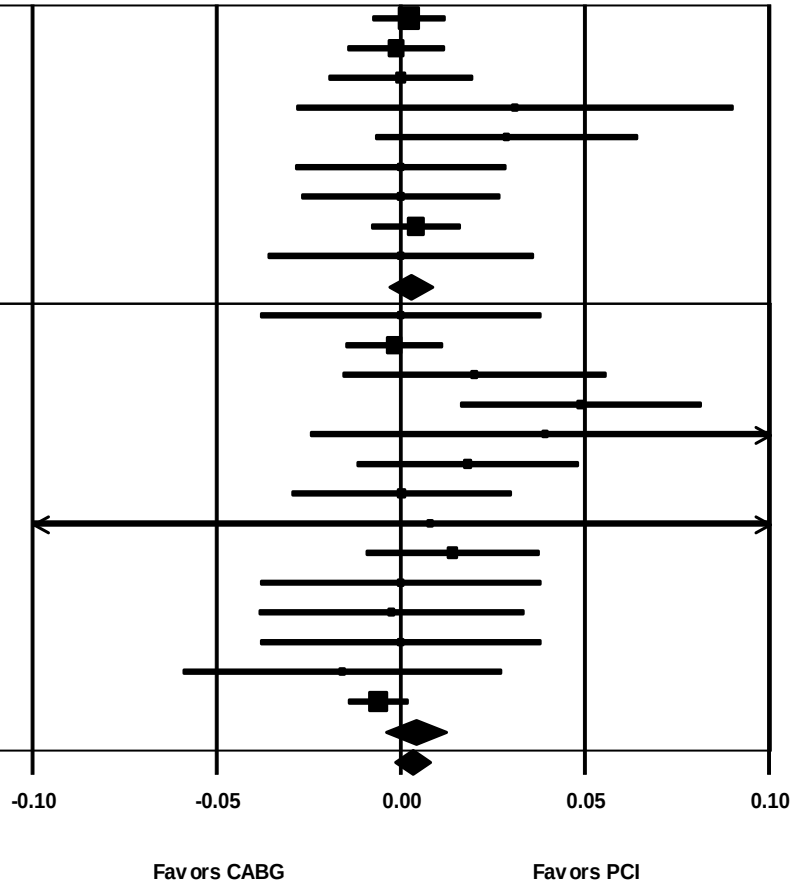
Table 9. Procedural survival reported in observational studies (continued)

Study Reference	Registry	Population	Inter-vention	Number of Patients	Demographics					Unadjusted Procedural Survival%
					Mean Age	Women %	White %	Diabetes %	Prior MI %	
Likosky et al.[202]	Northern New England	Patients undergoing isolated CABG between 1/1992 and 12/2001	CABG	31,592						96.6 [a]
Malenka et al.[201]	Northern New England	Patients with MVD who underwent PCI or CABG 1994-2001	PCI	4295	62.2	30.4		26.3	48.5	99.5*
			CABG	10198	64.5	26.7		34.4	44.7	98.3*
Mc Grath et al.[203]	Northern New England	Patients undergoing PCI 1990-1997	PCI 1990-1993	13,014	60.9	31.4		21.2	29.8	99.0
			PCI 1994-6/95	7,248	61.3	32.3		21.4	26.5	98.9[b]
			PCI 7/95-1997	14,490	61.9	32.4		22.3	23.5	98.8[b]
Hannan et al.[186]	NYSR	All patients in New York State undergoing PCI from 1/91-6/91	PCI	5827		29.6				99.4
Hannan et al.[187]	NYSR	All patients in New York State who underwent isolated PCI or CABG 1993-1995	PCI	29,930		32.0		17.4		99.6
			CABG	29,646		28.6		27.3		98.1
Hannan et al.[188]	NYSR	All patients in New York State who underwent PCI or CABG1997-2000	PCI	22,102	65**	31.4	87	25.3	27.4	99.3
			CABG	37,212	67**	29.1	89.2	33.2	25.0	98.2
Hannan et al.	NYSR	All patients in New York State who underwent CABG in 2002	CABG	16,120						97.7
Pell et al.[206]	Scottish	All patients in Scotland undergoing PCI or CABG between 4/97 and 3/99.	PCI	4775	61**	33		11		98.7
			CABG	5691	63**	24		12		96.8
Ferguson et al.[209]	STS	Patients undergoing isolated CABG from 1990-1999	CABG 1990	31,444	63.7	25.7	94.4	21.4	59	96.1[c]
			CABG 1999	182,407	65.1	28.7	89.8	32.7	49	97.0[c]
Steinbrook et al.[208]	STS	Patients undergoing CABG from 1996 to 2005	CABG 1996							96.8
			CABG 2005							97.8

[a]Adjusted Survival: CABG=96.6%; [b]Adjusted Survival: PCI 1990-1993=98.8%; PCI 1994-6/95=98.9%; PCI 7/95-1997=98.9%; [c]Adjusted Survival: CABG 1990=95.1%; CABG 1999=97.1%
*Adjusted procedural Survival; **Median; PCI=percutaneous coronary intervention; CABG=coronary artery bypass grafting; MVD=multi-vessel disease; VD=diseased vessels; MI=myocardial infarction; NYSR=New York State Registry; STS=Society of Thoracic Surgeons. The observational studies presented in this table were derived from our searches for representative registries and large administrative data, from our MEDLINE® search, and from expert advisors.

Figure 7. Comparing the procedural survival by final year of patient recruitment

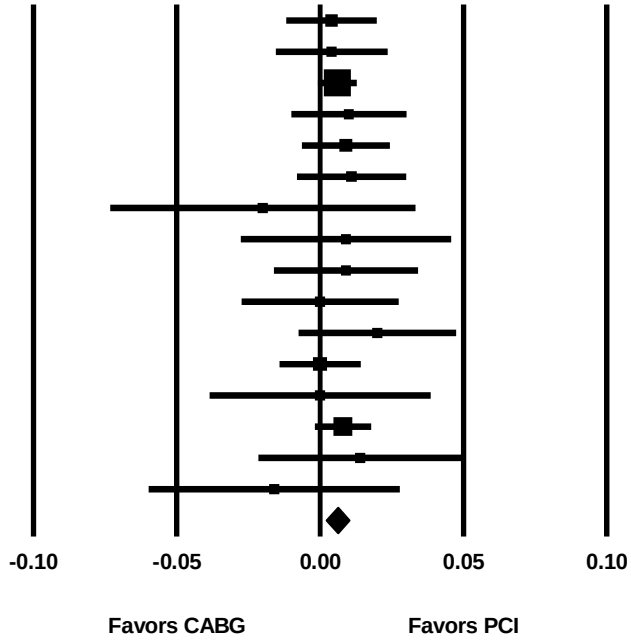
Study name	Risk difference	Lower limit	Upper limit	p-Value	PCI	CABG
BARI	0.002	-0.008	0.012	0.666	905 / 915	902 / 914
CABRI	-0.001	-0.015	0.012	0.855	534 / 541	507 / 513
EAST	0.000	-0.020	0.020	1.000	196 / 198	192 / 194
ERACI	0.031	-0.028	0.090	0.307	62 / 63	61 / 64
GABI	0.029	-0.007	0.064	0.116	179 / 182	169 / 177
Lausanne	0.000	-0.029	0.029	1.000	68 / 68	66 / 66
MASS	0.000	-0.027	0.027	1.000	72 / 72	70 / 70
RITA	0.004	-0.008	0.016	0.507	506 / 510	495 / 501
Toulouse	0.000	-0.036	0.036	1.000	75 / 76	75 / 76
Summary 1990-1993	0.003	-0.003	0.008	0.398	2597 / 2625	2537 / 2575
AMIST	0.000	-0.038	0.038	1.000	50 / 50	50 / 50
ARTS	-0.002	-0.015	0.012	0.794	591 / 600	597 / 605
AWESOME	0.020	-0.016	0.056	0.275	215 / 222	220 / 232
ERACI II	0.049	0.016	0.082	0.004	223 / 225	212 / 225
Groningen	0.039	-0.025	0.103	0.229	51 / 51	49 / 51
Leipzig	0.018	-0.012	0.048	0.239	110 / 110	108 / 110
MASS-II	0.000	-0.030	0.030	0.987	200 / 205	198 / 203
Myoprotect	0.008	-0.162	0.178	0.927	21 / 23	19 / 21
Octostent	0.014	-0.010	0.038	0.244	138 / 138	140 / 142
Poland	0.000	-0.038	0.038	1.000	50 / 50	50 / 50
Seoul-Hong	-0.003	-0.039	0.034	0.891	117 / 119	69 / 70
Seoul-Kim	0.000	-0.038	0.038	1.000	50 / 50	50 / 50
SIMA	-0.016	-0.059	0.028	0.474	62 / 63	60 / 60
SoS* Survival 1 month	-0.006	-0.014	0.002	0.150	484 / 488	499 / 500
Summary 1998-2003	0.004	-0.004	0.012	0.350	2363 / 2394	2322 / 2369
Summary for Procedural Survival	0.003	-0.002	0.008	0.218	4960 / 5019	4859 / 4944



1990-1993 Trials: Heterogeneity Statistics: Q-value 3.4, P-value 0.9; I-squared 0. PCI/CABG Odds ratio analysis: 1.36 (CI: 0.82,2.25; p=0.2)
1998-2003 Trials: Heterogeneity Statistics: Q-value 16.6, P-value 0.2; I-squared 22. PCI/CABG Odds ratio analysis: 1.39 (CI: 0.97,2.20; p=0.08)
Trial names followed by an asterisk indicate that the survival data were abstracted from Kaplan-Meier curves.
PCI=percutaneous coronary intervention; CABG=coronary artery bypass grafting; MVD=multi-vessel disease; CI=Confidence Interval

Figure 8. Freedom from procedural stroke

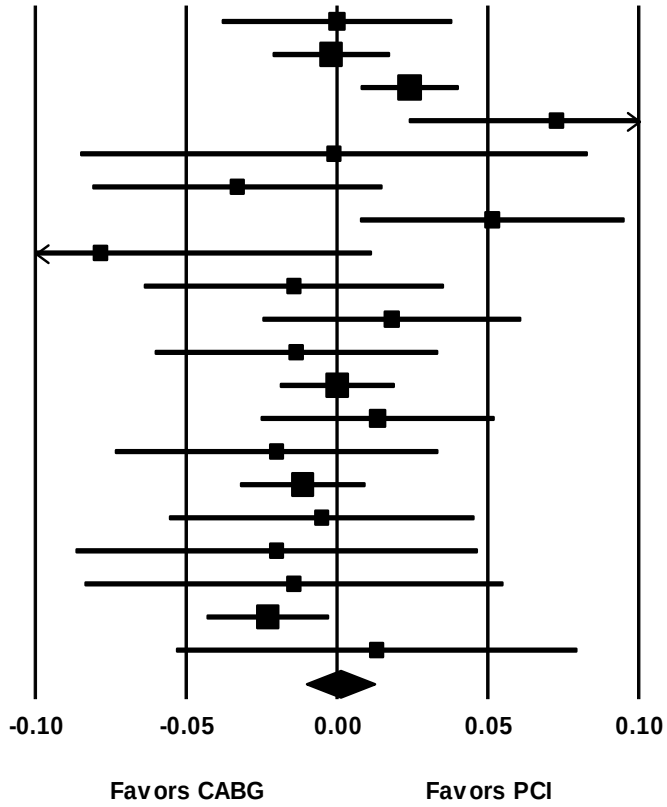
Study name	Risk fference	Lower limit	Upper limit	p-Value	PCI	CABG
ARTS	0.004	-0.011	0.019	0.611	590 / 600	592 / 605
AWESOME	0.004	-0.015	0.023	0.682	220 / 222	229 / 232
BARI	0.006	-0.000	0.012	0.069	913 / 915	907 / 914
EAST	0.010	-0.010	0.030	0.320	197 / 198	191 / 194
ERACI-II	0.009	-0.006	0.024	0.240	225 / 225	223 / 225
GABI	0.011	-0.008	0.030	0.249	182 / 182	175 / 177
Groningen	-0.020	-0.073	0.033	0.459	50 / 51	51 / 51
Lausanne	0.009	-0.027	0.045	0.627	68 / 68	65 / 66
Leipzig	0.009	-0.016	0.034	0.476	110 / 110	109 / 110
MASS	0.000	-0.027	0.027	1.000	72 / 72	70 / 70
MASS II	0.020	-0.007	0.047	0.149	203 / 205	197 / 203
Octostent	0.000	-0.014	0.014	1.000	138 / 138	142 / 142
Poland	0.000	-0.038	0.038	1.000	50 / 50	50 / 50
RITA	0.008	-0.002	0.018	0.100	509 / 510	496 / 501
Seoul-Hong	0.014	-0.021	0.049	0.435	119 / 119	69 / 70
SIMA	-0.016	-0.060	0.028	0.471	62 / 63	60 / 60
	0.006	0.002	0.010	0.002	3708 / 3728	3626 / 3670



Heterogeneity Statistics: Q-value 5.1, P-value 0.99; I-squared 0; PCI/CABG Odds Ratio Analysis: 1.96 (CI: 1.16, 329, p=0.01) PCI=percutaneous coronary intervention; CABG=coronary artery bypass grafting; CI=confidence interval

Figure 9. Freedom from procedural MI

Study name	Risk difference	Lower limit	Upper limit	p-Value	PCI	CABG
AMIST	0.000	-0.038	0.038	1.000	50 / 50	50 / 50
ARTS	-0.002	-0.021	0.018	0.847	581 / 600	587 / 605
BARI	0.024	0.008	0.040	0.004	896 / 915	873 / 914
EAST	0.073	0.024	0.122	0.004	192 / 198	174 / 194
ERACI	-0.001	-0.085	0.083	0.981	59 / 63	60 / 64
ERACI II	-0.033	-0.081	0.015	0.179	205 / 225	212 / 225
GABI	0.051	0.008	0.095	0.022	178 / 182	164 / 177
Groningen	-0.078	-0.168	0.012	0.088	46 / 51	50 / 51
Lausanne	-0.014	-0.064	0.036	0.575	66 / 68	65 / 66
Leipzig	0.018	-0.025	0.061	0.407	108 / 110	106 / 110
MASS	-0.013	-0.061	0.034	0.574	70 / 72	69 / 70
MASS-II	0.000	-0.019	0.019	0.992	203 / 205	201 / 203
Octostent	0.013	-0.025	0.052	0.497	135 / 138	137 / 142
Poland	-0.020	-0.074	0.034	0.465	49 / 50	50 / 50
RITA	-0.011	-0.032	0.010	0.287	492 / 510	489 / 501
Seoul-Hong	-0.005	-0.056	0.046	0.845	115 / 119	68 / 70
Seoul-Kim	-0.020	-0.087	0.047	0.557	48 / 50	49 / 50
SIMA	-0.014	-0.084	0.055	0.687	60 / 63	58 / 60
SoS	-0.023	-0.043	-0.003	0.027	469 / 488	492 / 500
Toulouse	0.013	-0.053	0.080	0.699	73 / 76	72 / 76
	0.001	-0.010	0.012	0.871	4095 / 4233	4026 / 4178



Heterogeneity Statistics: Q-value 35.7, P-value 0.01; I-squared 46.8

PCI=percutaneous coronary intervention; CABG=coronary artery bypass grafting; CI=Confidence Interval; MI=myocardial infarction

Long-Term Outcomes

Survival

Survival data from the individual RCTs are presented in a standard format (Figure 10) to facilitate comparison of long-term outcomes. Overall survival across all randomized trials did not differ significantly between CABG and PCI between one and five years of follow-up: PCI-CABG survival difference at each time point was less than 1 percent. We present the forest plots of survival at six months to five years in Appendix C Figures 6-15. The one- and five-year survival data for the 11 studies that reported survival at both of these intervals (Figure 11) demonstrated no significant difference between groups at these intervals.

Similarly, there was no significant difference in the comparative survival benefit in either the first or fifth year post-procedure between trials enrolling patients with single-vessel LAD disease and trials enrolling patients with multi-vessel disease (Figure 12).

Overall, the survival difference between PCI and CABG favored CABG in the older trials that employed balloon angioplasty and trended toward favoring PCI in the more recent trials that employed coronary stents (Appendix Figures 16-17). However, the recent trials included more patients with single-vessel LAD disease and had much shorter follow-up. In Figures 13 and 14, we present the survival differences between PCI and CABG separately for the single-vessel versus multi-vessel disease trials. At one year, in trials of single-vessel-LAD disease, survival in studies using balloon angioplasty was 1 percent greater for CABG recipients (CI: -5 percent to +2 percent) but was 0.1 percent greater for PCI recipients (CI: -4 percent to +4 percent) for trials using stents; these differences were not statistically significant. Similarly, among trials of multi-vessel disease, the survival difference at one year for balloon trials was 0.6 percent greater for CABG (CI: -1.5 percent to +0.4 percent) versus a survival difference among stent trials of 1.4 percent greater for PCI (CI: -1 percent to +3.8 percent); again, these differences were not statistically significant (Figure 13). The same pattern was also evident at five years (Figure 14). Odds ratios demonstrate the same trend found using risk differences.

To evaluate the generalizability of the RCT survival results in non-RCT settings, we examined survival data from registries associated with clinical trials. However, interpretation of these results is complicated by potential sources of bias in treatment allocation and the need for survival outcomes adjusted for key factors likely to affect mortality (e.g., age, co-morbid conditions, and severity of CAD). Three of the randomized trials (AWESOME, BARI, and EAST) reported the details of their screening as well as the characteristics and outcomes of the "eligible, not randomized" patients (Appendix C Tables 5 and 6), especially those who chose PCI. We note that these outcome data were not adjusted to reflect the differences in baseline characteristics. Survival in eligible, not randomized patients was better than that of randomized patients in two trials, but not in the third trial (Figure 15). It is, therefore, hard to draw general conclusions, especially since patients and their physicians may decline randomization based on the perception that the patient is either too sick or too well to leave the choice of therapy to chance.

Five major clinical registries[147, 157, 187, 201, 206] included more than 1000 PCI and 1000 CABG patients, reported long-term survival patterns, and used multivariable statistical methods to adjust for clinical differences in patients selected for PCI and CABG (Table 10). These registries reported striking differences in the patients selected for these two procedures, with most patients with single-vessel disease receiving PCI and most patients with triple-vessel disease receiving

CABG. Across the entire spectrum of disease severity, the CABG/PCI hazard ratio ranged from 0.48[206] to 0.86[201] favoring CABG. The CABG/PCI hazard ratio was significantly affected, however, by extent of coronary disease; in the Duke registry the CABG/PCI hazard ratio varied from 2.1 among patients with the least severe disease to 0.45 in patients with the most severe disease.[157] Similar variations in the hazard ratio according to severity of disease were reported by the Alberta,[147] Northern New England[201] and New York State[187] registries. In the patients with intermediate extent of disease who were most similar to patients enrolled in randomized trials, the clinical registries reported PCI/CABG hazard ratios were closer to 1.0.

Table 10. Long-term survival in major clinical registries

Name	Centers	Enrollment Interval	N PCI	N CABG	1VD	2VD	3VD	HR Overall CABG/PCI	HR Subgroup Range*
NY State[188]	35	1997-2000	22102	37212	0%	80%	20%	NR	0.64 to 0.75
NY State[187]	32	1993-1995	29930	29646	40%	28%	32%	NR	0.6 to 1.7
Duke[157]	1	1986-1990	2924	3890	37%	32%	32%	NR	0.4 to 2.1
N New England[201]	5	1994-2001	4295	10198	0%	60%	40%	0.86	0.60 to 0.98
Alberta[147]	4	1995-1998	3540	3782	0%	31%	70%	0.81	0.3 to 1.43
Scotland[206]	6	1997-1999	4775	5115	23%	18%	59%	0.48	NR

PCI=percutaneous coronary intervention; CABG=coronary artery bypass grafting; VD=vessels diseased; HR=hazard ratio; MVD=multi-vessel disease

*CABG/PCI Hazard Ratio from most severe to least coronary artery disease

Freedom from angina

Freedom from angina was more common after CABG than after PCI between one and five years post-procedure (PCI-CABG difference in freedom from angina ranged from -5 percent to -8 percent; PCI/CABG odds ratio ranged from 0.5 to 0.66, $p<0.0001$ at 1-, 3-, and 5-years) (Figure 16). At one year, freedom from angina was 75 percent in PCI-assigned patients and 84 percent in CABG-assigned patients. At five years, freedom from angina grew to 79 percent in PCI-assigned patients and remained 84 percent in CABG-assigned patients. It is uncertain whether the greater angina relief was due to more complete initial revascularization with surgery or because of restenosis after PCI.

The relationship between residual myocardial jeopardy (a measure of the completeness of revascularization) and freedom from angina after PCI or CABG was examined in the angiographic substudy of the BARI trial.[62, 213] At one year after randomization, myocardial jeopardy was significantly lower ($p<0.01$) in the sample of 135 patients randomized to CABG (14.1 percent) than in the sample of 135 patients randomized to PCI (25.5 percent). Freedom from angina at one year was in 88 percent of the CABG-assigned patients versus 70 percent of the PCI-assigned patients ($p=0.004$). Myocardial jeopardy on the one year angiogram was a significant predictor of angina at one year (PCI/CABG odds ratio 1.28 per 10 percent increment in jeopardy), but initial randomization assignment remained a significant predictor of angina even after adjustment for the degree of myocardial jeopardy, suggesting that additional mechanisms beyond completeness of revascularization may affect angina after CABG.[213] At five years of follow-up, progression of disease in the untreated coronary arteries was the predominant predictor of late angina in patients enrolled in the BARI angiographic substudy.[62]

Freedom from repeat revascularization

Individual randomized trials provide clear and consistent evidence that freedom from repeat coronary revascularization was much higher after CABG than after PCI (Figure 17). At 1-year, patients who received PCI required 23 percent more repeat procedures than CABG recipients ($p < 0.0001$) (PCI/CABG OR 0.11; CI: 0.07, 0.17). This difference climbed to 33 percent at five years ($p < 0.0001$) (PCI/CABG OR 0.13; CI: 0.11, 0.16). However, although the trials consistently favored CABG, they were statistically heterogeneous (Figure 17).

This gap between PCI and CABG was wider in trials that used balloon angioplasty than in more recent trials that used coronary stents (Figure 18 and Table 11). Nevertheless, patients undergoing PCI with stents require repeat procedures considerably more often than patients undergoing CABG.

Table 11. Absolute rates of freedom from repeat revascularization

Year Post-procedure	All Studies		Balloon-Era Trials		Stent-Era Trials	
	PCI	CABG	PCI	CABG	PCI	CABG
1	73.5%	96.2%	58.3%	96%	81.9%	96.3%
3	61.6%	91.6%	51.8%	88.1%	64.5%	92.9%
5	53.9%	90.2	51.5%	90.1%	59.9%	90.3%

PCI=percutaneous coronary intervention; CABG=coronary artery bypass grafting

Freedom from myocardial infarction

Ten studies reported myocardial infarction in follow-up (Appendix C Figure 18). Between one and five years after the procedure, freedom from myocardial infarction decreased among all patients, but at a somewhat higher rate for PCI recipients. However, the PCI-CABG differences in freedom from myocardial infarction were small (less than 1 percent) (PCI/CABG odds ratio ranged from 0.87 to 0.92) and did not achieve statistical significance.

Freedom from stroke

Seven studies reported freedom from stroke in follow-up (Table 12). These studies were heterogeneous in terms of the types of stroke reported (i.e., fatal, non-fatal, not specified) and in terms of their results. For example, at one year, two trials found greater freedom from strokes among PCI patients, one trial found great freedom from strokes among CABG patients, and two found no differences between the procedures. This heterogeneity and the paucity of studies reporting strokes beyond one year precludes us from drawing conclusions about the comparative effects of PCI and CABG on freedom from strokes after the initial procedural period.

Quality of life

Data on quality of life and functional status were collected by 11 trials (Table 13). The measures chosen were different from trial to trial, however, with the SF-36 or its subscales used by four studies, the Seattle Angina Questionnaire (SAQ) used by two studies, the Nottingham Health Profile by two studies, the EuroQol by two studies, and the Duke Activity Status Index (DASI) by one study. In general, these quality of life scores were higher among CABG patients

over one to three years of follow-up; however, many trials reported no significant differences between PCI and CABG recipients. Quality of life scores were strongly correlated with the presence and severity of angina in the RITA trial, and change in quality of life scores was significantly related to relief of angina in the BARI trial. Since generally accepted models suggest that symptoms mediate the effect of disease on quality of life, the comparative quality of life outcomes are consistent with the greater relief of angina by CABG over the first few years of follow-up.

Cognitive function

Several studies of CABG have used sensitive tests of cognitive function and documented declines from baseline to short-term follow-up (two to six weeks) after the procedure, with substantial recovery by three to six months. The mechanism responsible for this effect has not been fully established.

Despite the widespread concerns about cognitive function, only two PCI-CABG trials included detailed cognitive function testing. The BARI trial assessed cognitive function five years after randomization in a substudy of 125 patients.[73] There was no significant difference between PCI and CABG on any of the five measures of cognitive function (Logical and Figural Memory Scales, Wechsler Memory Scale, the Digit Symbol and Digit Span Subtests, and Part B of the Reitan Trail Making Test). The SOS Trial[141] measured a battery of five cognitive function tests in a substudy of 145 patients at baseline, six months and twelve months. There were no significant differences between PCI and CABG patients in follow-up on any of the measures (Digit Span Forward and Backward, Visual Reproduction, Bourdon, and Block Design). These two randomized substudies are too small to provide a definitive conclusion about the comparative effects of CABG and PCI on cognitive function.

Cost

Cost was examined in ten trials (Figure 19), although the methods of cost determination varied among these trials, which were conducted in the United States, Europe, and South America, and which have quite different health care systems. Consequently, we normalized costs by dividing the cumulative costs for PCI patients by the cumulative costs for CABG patients, which eliminates the variations in monetary units and in costing methods between trials. In all but one trial, PCI-assigned patients had much lower initial costs than CABG-assigned patients, but the difference in costs between PCI and CABG narrowed substantially over subsequent follow-up. (The exception to this was the ERACI trial which employed a different method of accounting for the cost of stents than was used in other trials.) In medium to long-term follow-up, PCI-assigned patients had only modestly lower costs (roughly 5 percent). These same trends are apparent in both balloon angioplasty trials and in trials that used coronary stents (Figure 19).

Other outcomes of interest

There were several additional long term outcomes that we were interested in for which neither the RCTs nor the registries provided data. These included information regarding the comparative effectiveness of PCI and CABG on congestive heart failure, chronic pulmonary

conditions, chronic renal failure, cardiac arrhythmias, target lesion revascularization, restenosis or graft closure, and readmission rates.

Quality of evidence for Key Question 1a

Given the large sample of generally consistent RCT results, the quality of the evidence addressing Key Question 1a was *robust* for most outcomes. However, MI and QOL were both rated *acceptable*; MI received this rating due to heterogeneity in the methods used to classify and assess patients for MI, and QOL received this rating due to inconsistency of findings across the studies. Cognitive function was rated *weak* given the paucity and heterogeneity of that literature.

Figure 10. Survival reported by each RCT

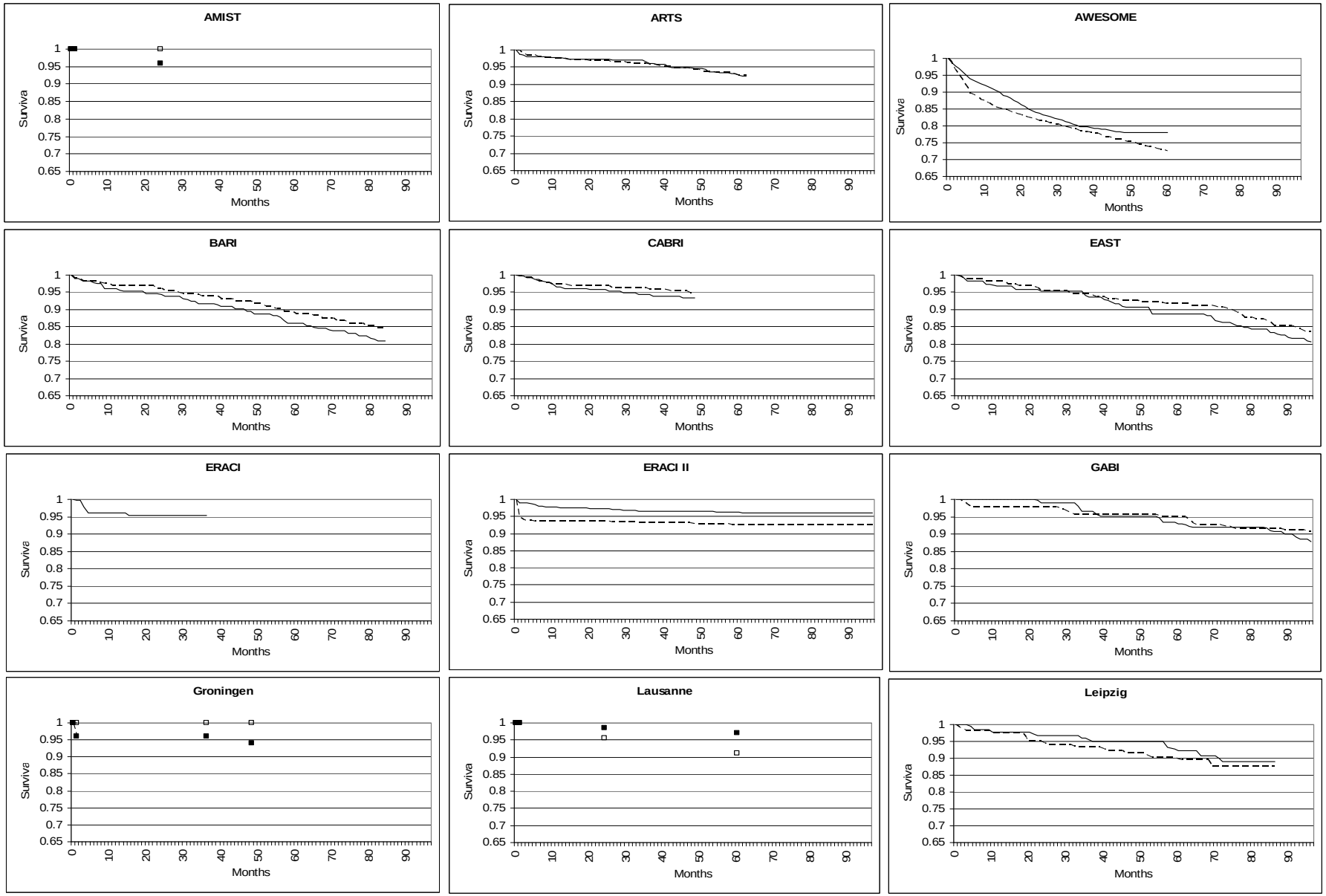
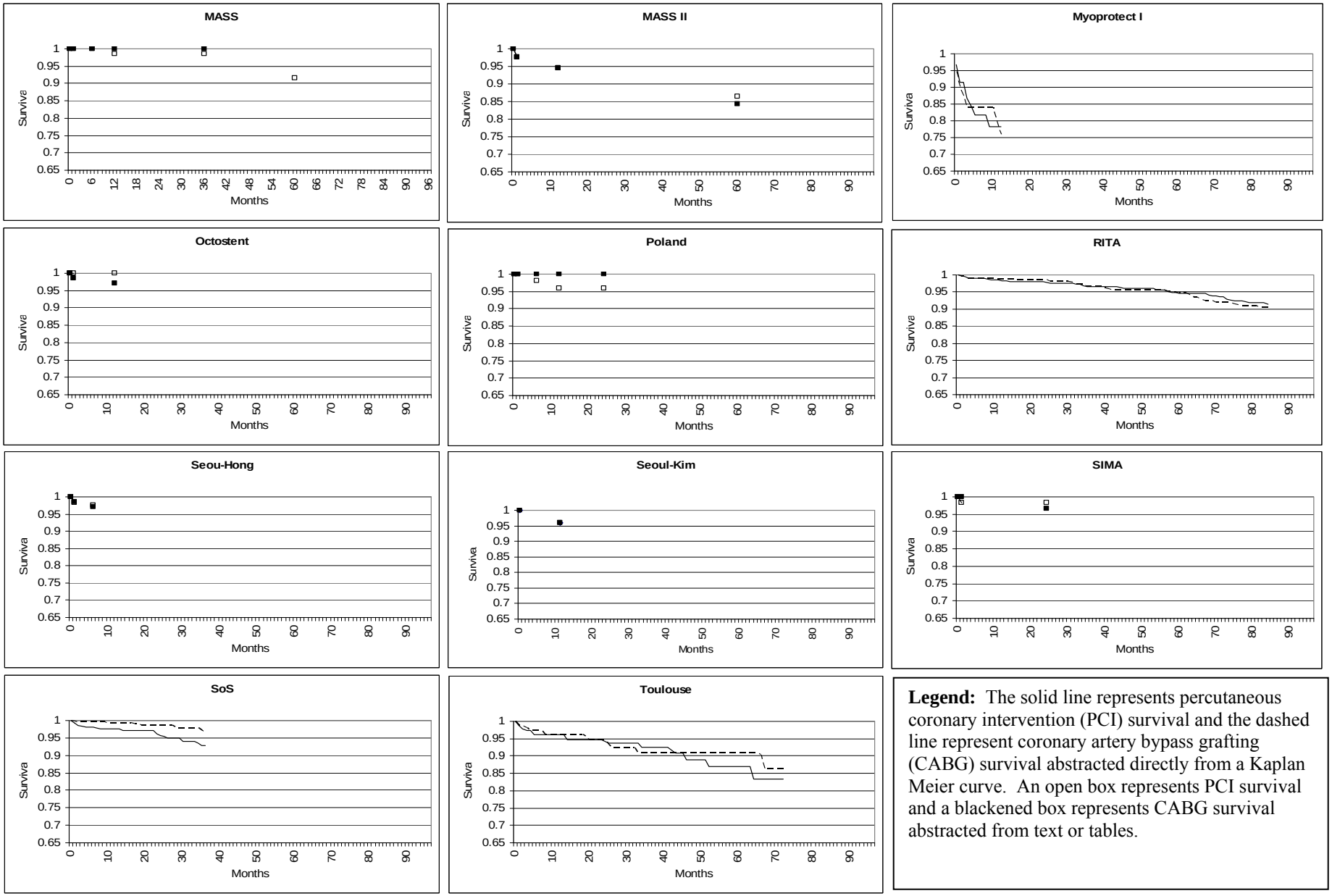


Figure 10. Survival reported by each RCT (continued)

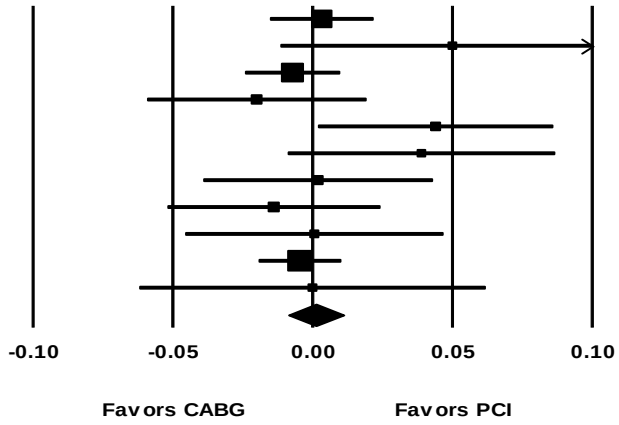


Legend: The solid line represents percutaneous coronary intervention (PCI) survival and the dashed line represent coronary artery bypass grafting (CABG) survival abstracted directly from a Kaplan Meier curve. An open box represents PCI survival and a blackened box represents CABG survival abstracted from text or tables.

Figure 11. PCI-CABG survival difference from the 11 RCTs reporting both 1 and 5 year survival data

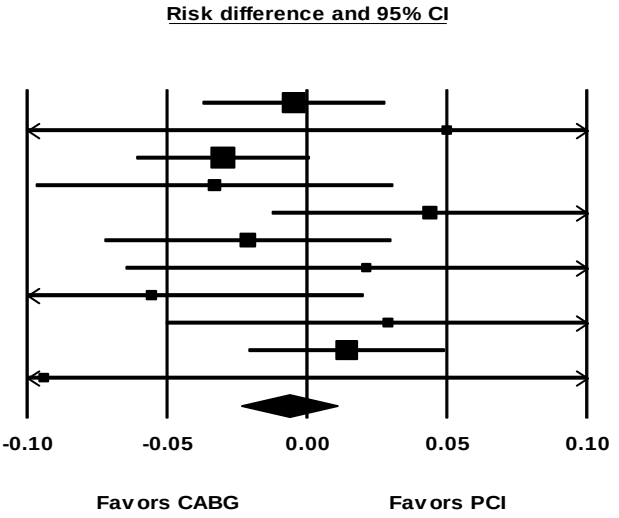
At 1-Year: Summary PCI-CABG Survival Difference: 0.1 %(CI: -0.9%, 1.1%); Summary PCI/CABG Odds ratio: 1.13 (CI: 0.86, 1.49)

Study name	Risk difference	Lower limit	Upper limit	p-Value	Survival / Total PCI	Survival / Total CABG
ARTS	0.003	-0.015	0.022	0.731	570 / 585	571 / 588
AWESOME	0.050	-0.012	0.112	0.111	189 / 208	175 / 203
BARI*	-0.007	-0.024	0.010	0.408	879 / 915	884 / 914
EAST	-0.020	-0.059	0.019	0.318	181 / 191	184 / 190
ERACI II	0.044	0.002	0.086	0.041	216 / 223	196 / 212
GABI	0.039	-0.009	0.087	0.111	151 / 155	130 / 139
Leipzig*	0.002	-0.039	0.043	0.925	107 / 110	103 / 106
MASS	-0.014	-0.052	0.024	0.476	70 / 71	70 / 70
MASS-II	0.001	-0.046	0.047	0.980	183 / 194	181 / 192
RITA*	-0.005	-0.019	0.010	0.547	497 / 506	489 / 495
Toulouse*	-0.000	-0.062	0.062	0.999	70 / 73	68 / 71
	0.001	-0.009	0.011	0.835	3115 / 3231	3052 / 3180



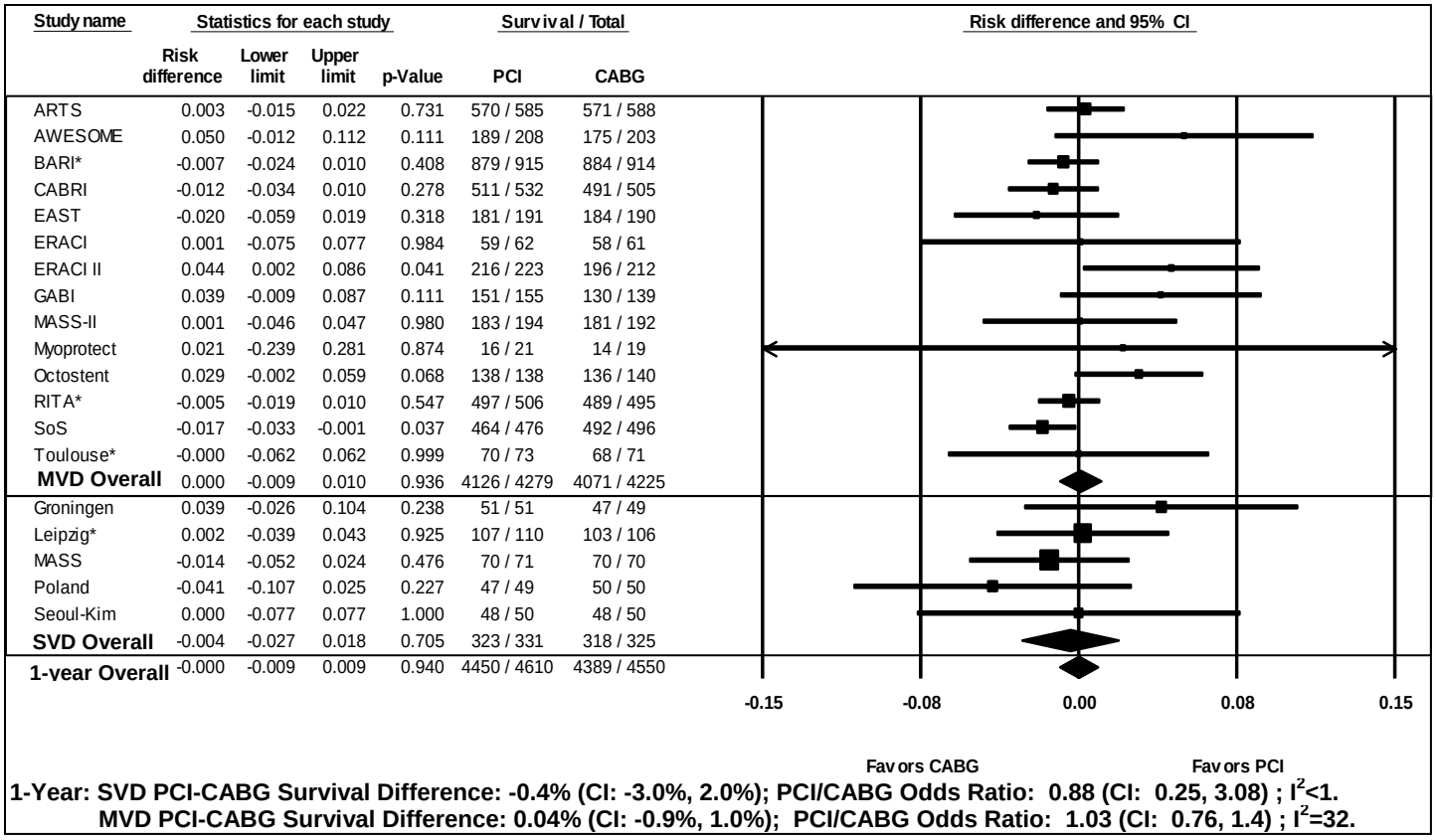
At 5-Years: Summary PCI-CABG Survival Difference: -0.6% (CI: -2.4%, 1.1%); Summary PCI/CABG Odds ratio: 0.94 (CI: 0.78, 1.14)

Study name	Risk difference	Lower limit	Upper limit	p-Value	Survival / Total PCI	Survival / Total CABG
ARTS	-0.005	-0.037	0.028	0.780	504 / 552	513 / 559
AWESOME	0.050	-0.166	0.266	0.649	30 / 38	19 / 26
BARI	-0.030	-0.061	0.001	0.059	727 / 842	768 / 860
EAST	-0.033	-0.097	0.031	0.312	153 / 174	161 / 177
ERACI II	0.044	-0.013	0.101	0.128	194 / 209	176 / 199
GABI*	-0.021	-0.072	0.030	0.421	161 / 173	148 / 156
Leipzig	0.021	-0.065	0.107	0.629	95 / 106	91 / 104
MASS	-0.056	-0.131	0.020	0.151	65 / 71	67 / 69
MASS-II	0.029	-0.050	0.108	0.475	149 / 177	139 / 171
RITA	0.014	-0.021	0.049	0.428	455 / 494	438 / 483
Toulouse	-0.094	-0.309	0.121	0.393	21 / 31	27 / 35
	-0.006	-0.024	0.011	0.457	2553 / 2867	2548 / 2839

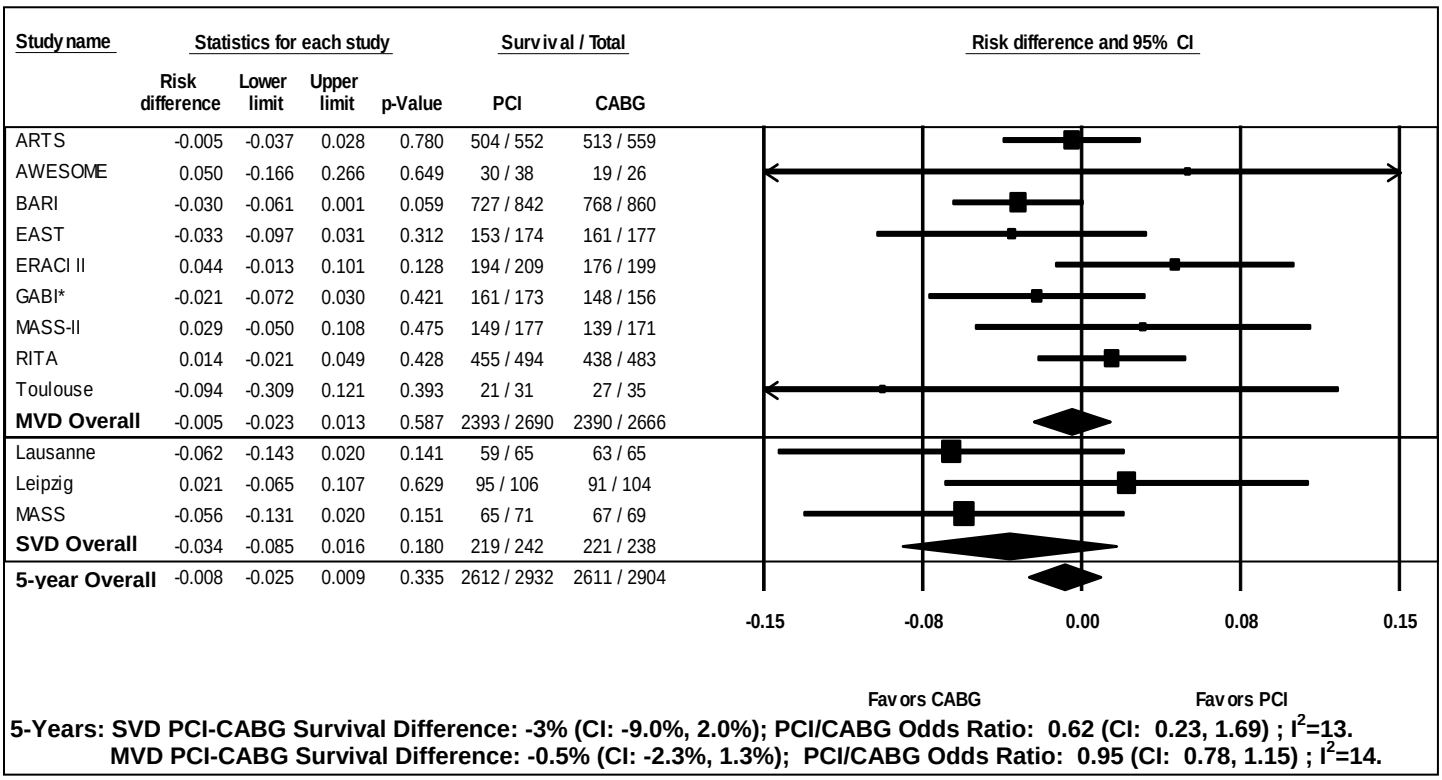


Trial names followed by an asterisk indicate that the survival data were abstracted from Kaplan-Meier curves.
PCI=percutaneous coronary intervention; CABG=coronary artery bypass grafting; CI=confidence interval

Figure 12. Comparison of single (SVD) with multi-vessel (MVD) survival at 1 and 5 years



1-Year: SVD PCI-CABG Survival Difference: -0.4% (CI: -3.0%, 2.0%); PCI/CABG Odds Ratio: 0.88 (CI: 0.25, 3.08) ; I^2<1.
MVD PCI-CABG Survival Difference: 0.04% (CI: -0.9%, 1.0%); PCI/CABG Odds Ratio: 1.03 (CI: 0.76, 1.4) ; I^2=32.

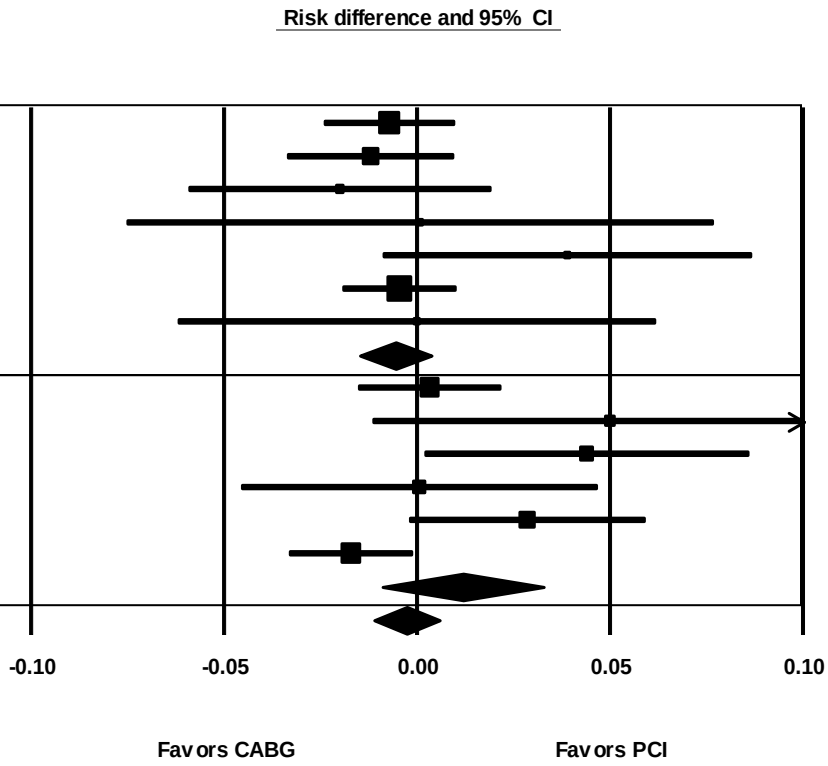


5-Years: SVD PCI-CABG Survival Difference: -3% (CI: -9.0%, 2.0%); PCI/CABG Odds Ratio: 0.62 (CI: 0.23, 1.69) ; I^2=13.
MVD PCI-CABG Survival Difference: -0.5% (CI: -2.3%, 1.3%); PCI/CABG Odds Ratio: 0.95 (CI: 0.78, 1.15) ; I^2=14.

Trial names followed by an asterisk indicate that the survival data were abstracted from Kaplan-Meier curves.
PCI=percutaneous coronary intervention; CABG=coronary artery bypass grafting; CI=confidence interval

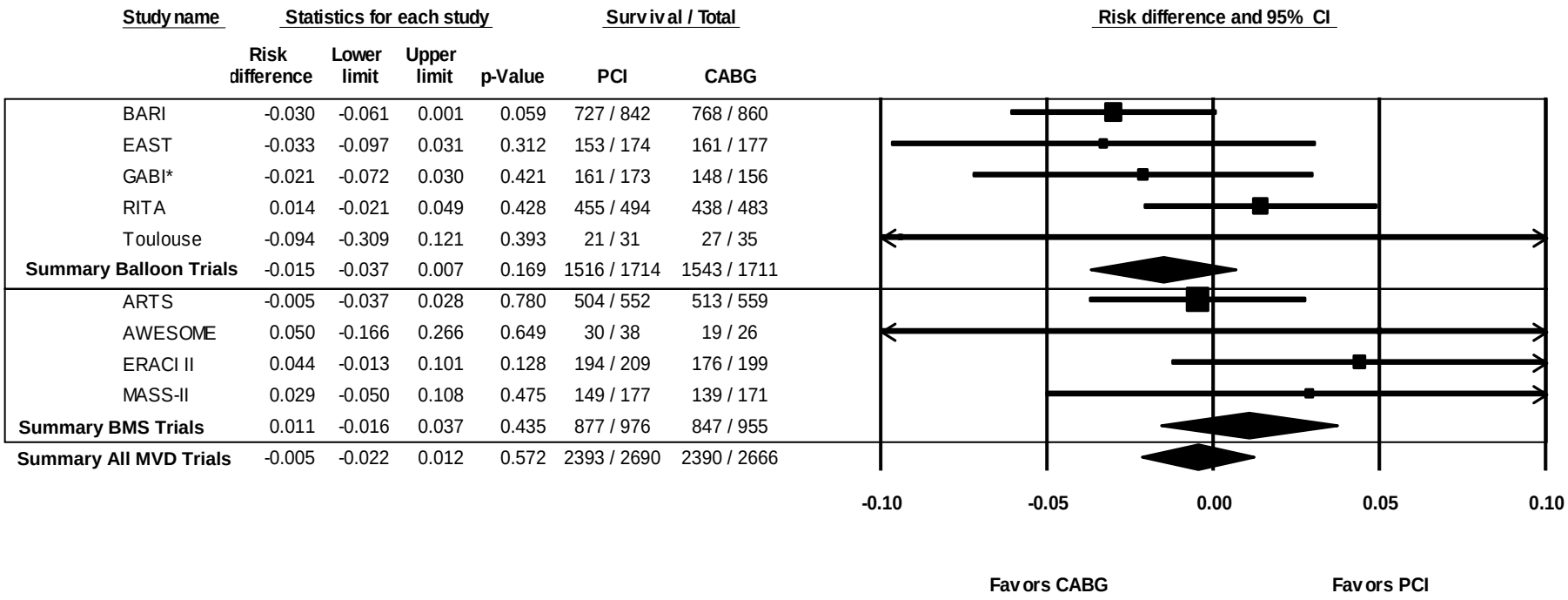
Figure 13. Comparison of one-year survival in balloon angioplasty or stents versus CABG in patients with MVD

Study name	Statistics for each study				Survival / Total	
	Risk difference	Lower limit	Upper limit	p-Value	PCI	CABG
BARI*	-0.007	-0.024	0.010	0.408	879 / 915	884 / 914
CABRI	-0.012	-0.034	0.010	0.278	511 / 532	491 / 505
EAST	-0.020	-0.059	0.019	0.318	181 / 191	184 / 190
ERACI	0.001	-0.075	0.077	0.984	59 / 62	58 / 61
GABI	0.039	-0.009	0.087	0.111	151 / 155	130 / 139
RITA*	-0.005	-0.019	0.010	0.547	497 / 506	489 / 495
Toulouse*	-0.000	-0.062	0.062	0.999	70 / 73	68 / 71
Summary Balloon Trials	-0.006	-0.015	0.004	0.224	2349 / 2434	2305 / 2375
ARTS	0.003	-0.015	0.022	0.731	570 / 585	571 / 588
AWESOME	0.050	-0.012	0.112	0.111	189 / 208	175 / 203
ERACI II	0.044	0.002	0.086	0.041	216 / 223	196 / 212
MASS-II	0.001	-0.046	0.047	0.980	183 / 194	181 / 192
Octostent	0.029	-0.002	0.059	0.068	138 / 138	136 / 140
SoS	-0.017	-0.033	-0.001	0.037	464 / 476	492 / 496
Summary BMS Trials	0.012	-0.009	0.033	0.272	1760 / 1824	1751 / 1831
Summary All MVD Trials	-0.003	-0.011	0.006	0.506	4110 / 4258	4056 / 4206



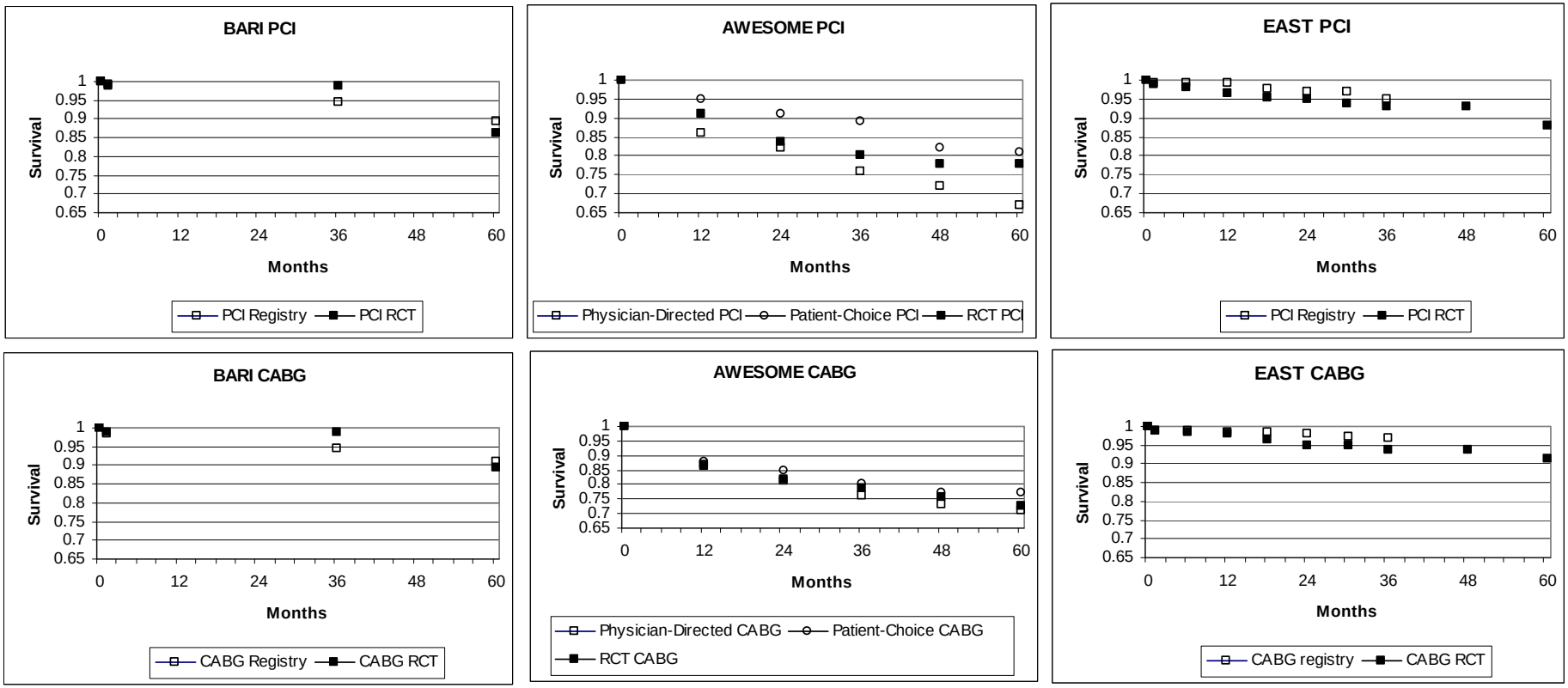
Balloon Trials: Summary PCI/CABG Odds Ratio: 0.83 (CI: 0.60, 1.15)
Bare Metal Stent Trials: Summary PCI/CABG Odds Ratio: 1.32 (CI: 0.66, 2.64)
Trial names followed by an asterisk indicate that the survival data were abstracted from Kaplan-Meier curves.
PCI=percutaneous coronary intervention; CABG=coronary artery bypass grafting; MVD=multi-vessel disease; CI=confidence interval

Figure 14. Comparison of five-year survival in balloon angioplasty or stents versus CABG in patients with MVD



Balloon Trials: Summary PCI/CABG Odds Ratio: 0.83 (CI: 0.66, 1.03)
Bare Metal Stent Trials: Summary PCI/CABG Odds Ratio: 1.51 (CI: 0.86, 1.54)
Trial names followed by an asterisk indicate that the survival data were abstracted from Kaplan-Meier curves.
PCI=percutaneous coronary intervention; CABG=coronary artery bypass grafting; MVD=multi-vessel disease; CI=confidence interval

Figure 15. Comparison of survival between RCTs and registries (AWESOME, BARI, and EAST)

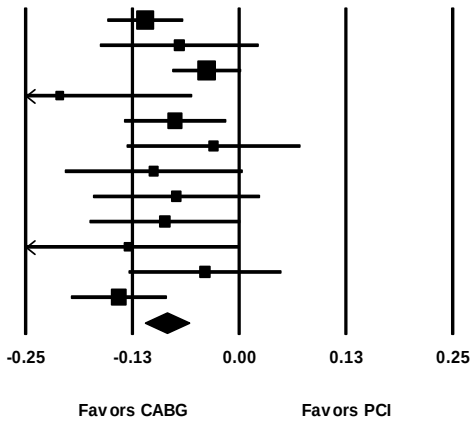


RCT=randomized controlled trial; PCI=percutaneous coronary intervention; CABG=coronary artery bypass grafting

Figure 16. Angina relief

One Year

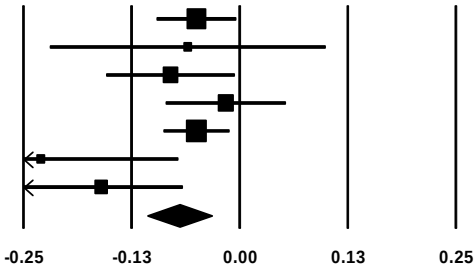
Study name	Risk difference	Lower limit	Upper limit	p-Value	PCI	CABG
ARTS	-0.110	-0.155	-0.065	0.000	367 / 464	509 / 566
AWESOME	-0.070	-0.163	0.023	0.141	116 / 166	137 / 178
CABRI	-0.038	-0.078	0.002	0.065	432 / 502	436 / 485
ERACI	-0.210	-0.365	-0.055	0.008	38 / 62	50 / 61
ERACI II	-0.075	-0.135	-0.015	0.014	188 / 223	195 / 212
GABI	-0.030	-0.132	0.072	0.565	110 / 155	103 / 139
Lausanne	-0.100	-0.204	0.004	0.060	57 / 68	62 / 66
MASS-II	-0.073	-0.171	0.024	0.141	107 / 194	120 / 192
Octostent	-0.087	-0.176	0.002	0.054	108 / 138	122 / 140
Seoul-Kim	-0.130	-0.260	-0.000	0.050	39 / 48	45 / 48
SIMA	-0.040	-0.130	0.050	0.382	57 / 63	57 / 60
SoS	-0.141	-0.197	-0.084	0.000	309 / 488	387 / 500
	-0.085	-0.111	-0.059	0.000	1929 / 2571	2223 / 2647



Heterogeneity statistics: Q-value 15.5, p-value 0.16, I-squared 29.
PCI/CABG Odds Ratio Analyis: 0.56 (CI: 0.48, 0.66; p< 0.0001).

Three Years

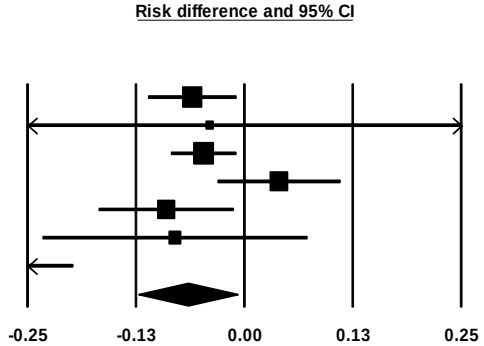
Study name	Risk difference	Lower limit	Upper limit	p-Value	PCI	CABG
ARTS	-0.050	-0.096	-0.004	0.034	346 / 422	471 / 541
AWESOME	-0.060	-0.220	0.100	0.462	40 / 67	49 / 75
EAST	-0.080	-0.155	-0.005	0.036	147 / 184	160 / 182
ERACI	-0.016	-0.086	0.054	0.653	57 / 60	59 / 61
ERACI II	-0.050	-0.088	-0.012	0.011	207 / 223	208 / 212
Groningen	-0.230	-0.389	-0.071	0.005	33 / 51	43 / 49
MASS	-0.160	-0.255	-0.065	0.001	59 / 72	69 / 70
	-0.070	-0.107	-0.033	0.000	889 / 1079	1058 / 1190



Heterogeneity statistics: Q-value 10.9, p-value 0.09, I-squared 44.9.
PCI/CABG Odds Ratio Analyis: 0.00 (CI: 0.0, 0.0; p= 0.001).

Five Years

Study name	Risk difference	Lower limit	Upper limit	p-Value	PCI	CABG
ARTS	-0.060	-0.111	-0.009	0.022	302 / 382	434 / 511
AWESOME	-0.040	-0.415	0.335	0.834	7 / 12	9 / 15
BARI	-0.047	-0.085	-0.009	0.015	619 / 777	664 / 787
ERACI II	0.040	-0.031	0.111	0.271	180 / 209	163 / 199
Leipzig	-0.090	-0.168	-0.012	0.024	91 / 106	99 / 104
MASS	-0.080	-0.233	0.073	0.305	46 / 71	50 / 69
Toulouse	-0.402	-0.607	-0.197	0.000	15 / 31	31 / 35
	-0.065	-0.122	-0.008	0.025	1260 / 1588	1451 / 1720



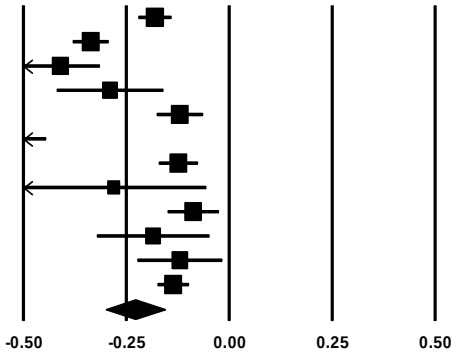
Heterogeneity statistics: Q-value 18.8, p-value 0.004, I-squared 68.0
PCI/CABG Odds Ratio Analyis: 0.66 (CI: 0.46, 0.95; p= 0.03).

PCI=percutaneous coronary intervention; CABG=coronary artery bypass grafting; CI=confidence interval

Figure 17. Freedom from repeat revascularization

One Year

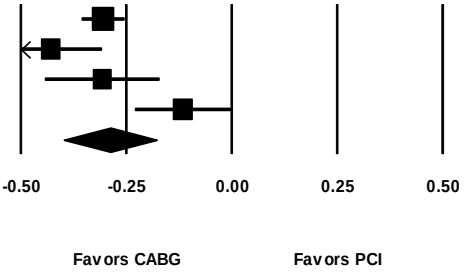
Study name	Risk difference	Lower limit	Upper limit	p-Value	Survival / Total PCI	Survival / Total CABG
ARTS	-0.181	-0.221	-0.140	0.000	363 / 464	545 / 566
CABRI	-0.337	-0.381	-0.292	0.000	334 / 532	487 / 505
EAST	-0.410	-0.506	-0.314	0.000	62 / 110	180 / 186
ERACI	-0.290	-0.419	-0.160	0.000	41 / 62	58 / 61
ERACI II	-0.120	-0.177	-0.063	0.000	186 / 223	202 / 212
GABI	-0.530	-0.615	-0.444	0.000	64 / 155	148 / 157
MASS-II	-0.124	-0.172	-0.075	0.000	169 / 194	191 / 192
Myoprotect	-0.281	-0.506	-0.055	0.015	14 / 21	18 / 19
Octostent	-0.087	-0.150	-0.025	0.006	121 / 138	135 / 140
Poland	-0.185	-0.322	-0.048	0.008	37 / 49	47 / 50
Seoul-Kim	-0.120	-0.224	-0.016	0.023	43 / 50	49 / 50
SoS	-0.136	-0.175	-0.098	0.000	391 / 476	475 / 496
	-0.229	-0.300	-0.157	0.000	1824 / 2474	2535 / 2634



Heterogeneity statistics: Q-value 157.6, p-value <0.0001; I-squared 93.
PCI/CABG Odds Ratio Analyis: 0.11 (CI: 0.07, 0.17; p< 0.0001).

Three Years

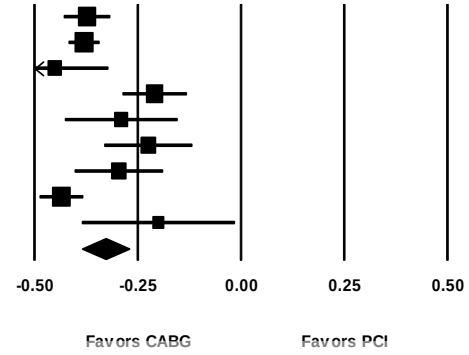
Study name	Risk difference	Lower limit	Upper limit	p-Value	PCI	CABG
ARTS	-0.305	-0.356	-0.254	0.000	262 / 422	501 / 541
EAST	-0.429	-0.551	-0.307	0.000	34 / 79	135 / 157
ERACI	-0.307	-0.444	-0.170	0.000	38 / 60	57 / 61
Groningen	-0.116	-0.230	-0.002	0.046	43 / 51	47 / 49
	-0.289	-0.399	-0.179	0.000	377 / 612	740 / 808



Heterogeneity statistics: Q-value 14.3, p-value 0.03; I-squared 79.0.
PCI/CABG Odds Ratio Analyis: 0.13 (CI: 0.01, 0.18; p< 0.0001).

Five Years

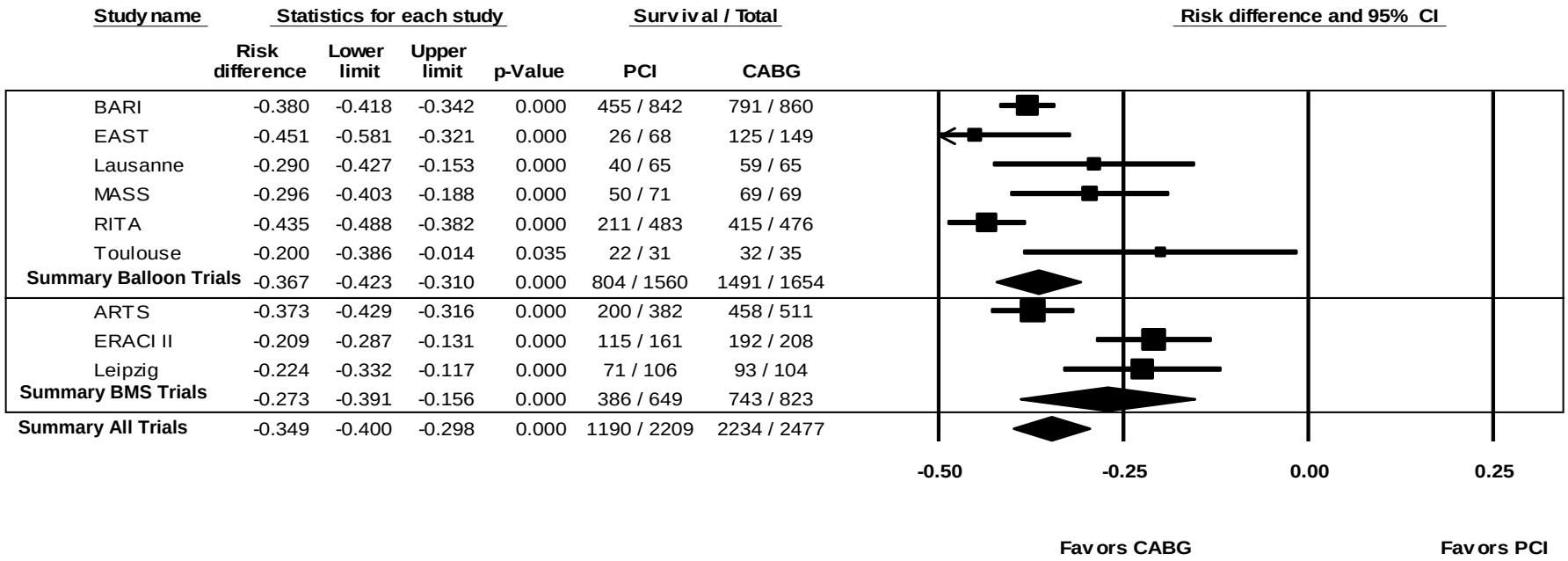
Study name	Risk difference	Lower limit	Upper limit	p-Value	Survival / Total PCI	Survival / Total CABG
ARTS	-0.373	-0.429	-0.316	0.000	200 / 382	458 / 511
BARI	-0.380	-0.418	-0.342	0.000	455 / 842	791 / 860
EAST	-0.451	-0.581	-0.321	0.000	26 / 68	125 / 149
ERACI II	-0.209	-0.287	-0.131	0.000	115 / 161	192 / 208
Lausanne	-0.290	-0.427	-0.153	0.000	40 / 65	59 / 65
Leipzig	-0.224	-0.332	-0.117	0.000	71 / 106	93 / 104
MASS	-0.296	-0.403	-0.188	0.000	50 / 71	69 / 69
RITA	-0.435	-0.488	-0.382	0.000	211 / 483	415 / 476
Toulouse	-0.200	-0.386	-0.014	0.035	22 / 31	32 / 35
	-0.329	-0.386	-0.272	0.000	1190 / 2209	2234 / 2477



Heterogeneity statistics: Q-value 36.3, p-value <0.0001; I-squared 77.9.
PCI/CABG Odds Ratio Analyis: 0.13 (CI: 0.11, 0.16; p< 0.0001).

PCI=percutaneous coronary intervention; CABG=coronary artery bypass grafting; CI=confidence interval

Figure 18. Freedom from repeat revascularization at 5 years: balloon angioplasty or stents versus CABG trials



Balloon trials: Heterogeneity statistics: Q-value 12.7, p-value 0.02; I-squared 60.7. PCI/CABG odds ratio analysis: 0.11 (CI: 0.09, 0.14; p<0.0001)
Bare metal stent (BMS) trials: Heterogeneity statistics: Q-value 13.4, p-value 0.001; I-squared 85.1. PCI/CABG odds ratio analysis: 0.15 (CI: 0.12, 0.20; p<0.0001)
PCI=percutaneous coronary intervention; CABG=coronary artery bypass grafting; CI=confidence interval

Table 12. Long-term freedom from stroke

Trial	Procedure	N at randomization	Procedural (%)	6 months (%)	Year 1 (%)	Year 2 (%)	Year 3 (%)	Year 4 (%)	Year 5 (%)
ARTS	PCI	600	590 (98.3)	590 (98.3)*	590 (98.3)		580 (96.7)		577 (96.1)
	CABG	605	592 (97.9)	592 (97.9)*	592 (97.9)		585 (96.7)		584 (96.5)
Groningen	PCI	51	50 (98.0)	50 (98.0)*	50 (98.0)*	50 (98.0)*	50 (98.0)	49 (96.1)	
	CABG	51	51 (100)	51 (100)*	51 (100)*	51 (100)*	51 (100)	51 (100)	
Leipzig	PCI	110	110 (100)	108 (98.2)					
	CABG	110	109 (99.1)	109 (99.1)					
MASS	PCI	72	72 (100)						71 free from fatal stroke
	CABG	70	70 (100)						70 free from fatal stroke
Octostent	PCI	138	138 (100)	138 (100)*	138 (100)				
	CABG	142	142 (100)	142 (100)*	142 (100)				
Poland	PCI	50	50 (100)*	50 (100)	50 (100)	50 (100)			
	CABG	50	50 (100)*	50 (100)	50 (100)	50 (100)			
SoS	PCI	488			481(98.6) free from non-fatal strokes				
	CABG	500			492 (98.4) free from non-fatal strokes				

Note: Most studies did not specify fatal or non-fatal strokes, those that did are so noted.
*Data marked with an asterisk were imputed from knowing that the stroke risk did not change between the preceding and subsequent time intervals.

Table 13. Quality of life information reported by randomized controlled trials

Trial	Instrument	Measure	Time point	PCI	CABG	Intervention Favored
ARTS	Visual Analog Scale	Average Thermometer (VAS 0-100)	Year 1	78	80	NS
ARTS	Euroqol	Average Summary (mobility, self-care, usual activity, pain or discomfort, anxiety or depression; scale 0-100)	Year 1	86	87	NS
AWESOME	SF-36	Physical component summary score (mean)	6 months	38.7	37.3	NS
AWESOME	SF-36	Mental component summary score (mean)	6 months	45.5	46.1	NS
CABRI	Nottingham Health Profile (part I)	Total Score	Baseline to Year 1	-8.7 +/-16.9	-11.9 +/-19.5	NS
		Emotional reaction (change in score)	Baseline to Year 1	-8.3 +/- 20.7	-8.4 +/- 25.0	NS
		Sleep (change in score)	Baseline to Year 1	-2.6 +/- 31.4	-13.7 +/- 33.4	NS
		Energy (change in score)	Baseline to Year 1	-17.3 +/- 38.1	-28.8 +/- 39.3	CABG[§]
		Pain (change in score)	Baseline to Year 1	-9.6 +/- 25.8	-11.1 +/- 21.5	NS
		Physical mobility (change in score)	Baseline to Year 1	-7.0 +/- 16.0	-7.3 +/- 21.5	NS
		Social relations (change in score)	Baseline to Year 1	-6.0 +/- 20.5.	-3.7 +/- 26.0	NS
CABRI*	Nottingham Health Profile (part II); % change in perceived health problems	At work	Baseline to Year 1	15	20	NS
		Household chores	Baseline to Year 1	21	22	NS
		Social life	Baseline to Year 1	13	15	NS
		Family life	Baseline to Year 1	8	14	NS
Myoprotect I	SF-12	Questionnaire score (mean)	Year 1	32.8 +/- 9	30.6 +/- 8	NS
Octostent		Quality-adjusted life years	Year 1	0.82	0.79	NS
Octostent	Euroqol	Summary score (estimated)	Year 1	0.82	0.83	NS
Octostent	SF-36		6 months*			
			Year 1**			
RITA	Nottingham Health Profile (Part I)	Mean Quality of Life (energy, pain, emotional reaction, sleep, social isolation and mobility) (change in score)	6 months	4.83	6.04	CABG[§]
			12 months	At 12 months, the difference between PCI and CABG in score change was 0.79, with CABG patients having a larger change		NS
SIMA	SF-36		9-15 months*			
	SAQ	Physical Limitation	9-15 months	86	91	NS
		Quality of Life	9-15 months	79	76	NS

Table 13. Quality of life information reported by randomized controlled trials (continued)

Trial	Instrument	Measure	Time point	PCI	CABG	Intervention Favored
EAST		Able to engage in moderate or strenuous activity	Year 3	47	44	NS
		Overall health good or very good	Year 3	61.1	64	NS
		Complete recovery	Year 3	58.7	69	NS
SoS	SAQ	Physical Limitation	6 months	73.6	76	NS
		Quality of Life	6 months	65.4	69	CABG[§]
		Physical Limitation	Year 1	75.2	76	NS
		Quality of Life	Year 1	69.8	71	NS
AMIST	SAQ	Physical Limitation	6 months	76.3	78.6	NS
		Quality of Life	6 months	68.1	68	NS
		Physical Limitation	Year 1	80.4	81	NS
		Quality of Life	Year 1	72.6	71.5	NS
	SF-36	Physical Component Summary Score	6 months	37.4	38.0	NS
		Mental Component Summary Score	6 months	51.1	52.4	NS
		Physical Component Summary Score	Year 1	37.7	39.4	NS
		Mental Component Summary Score	Year 1	51.4	55.0	CABG[§]
	Euroqol	Utility	6 months	0.78	0.80	NS
		Health Status	6 months	74.3	79.7	NS
		Utility	Year 1	0.77	0.82	NS
		Health Status	Year 1	74.6	81.7	NS

Table 13. Quality of life information reported by randomized controlled trials (continued)

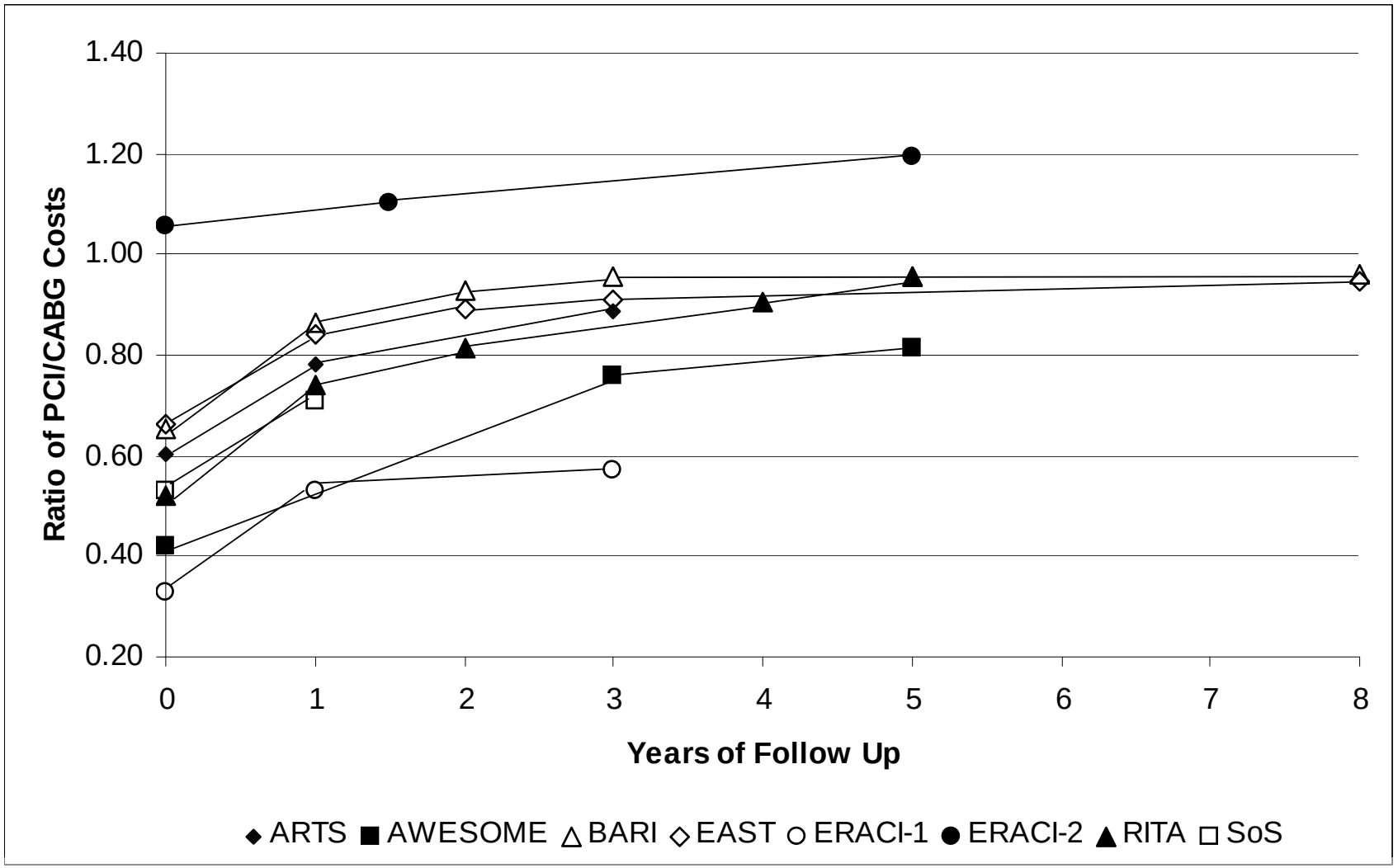
Trial	Instrument	Measure	Time point	PCI	CABG	Intervention Favored
BARI	Duke Activity Status Index	(change in score)	Year 1	4.4	7.0	CABG[§]
		(change in score)	Year 2	3.2	5.5	CABG[§]
		(change in score)	Year 3	3.2	5.6	CABG[§]
		(change in score)	Year 4	2.6	4.3	NS
		(change in score)	Year 5	2.0	3.6	NS
	Nottingham Health Profile (Part II); % change in perceived health problems	At work	Year 1	25	20	NS
		Household chores	Year 1	32	28	CABG[§]
		Social life	Year 1	19	17	NS
		Family life	Year 1	16	13	NS
		At work	Year 3	19	22	NS
		Household chores	Year 3	37	35	NS
		Social life	Year 3	24	22	NS
		Family life	Year 3	19	18	NS
		At work	Year 5	16	16	Neither
		Household chores	Year 5	40	36	NS
		Social life	Year 5	27	27	Neither
		Family life	Year 5	20	19	NS
	RAND Mental Health Inventory	(change in score)	Year 1	1.8	1.8	Neither

PCI=percutaneous coronary intervention; CABG=coronary artery bypass grafting; NS=no significant difference between PCI and CABG; [§] $p<0.05$

*No summary scores were provided; however, the scores on each section are available in the text. There was no statistically significant difference between PCI and CABG scores in any domain.

** No summary scores were provided; however, the scores in each domain are available in the text. Patients in the CABG group scored significantly higher ($p=0.03$) than patients in the PCI group in the domain of General Health Perception.

Figure 19. Comparative cost data



PCI=percutaneous coronary intervention; CABG=coronary artery bypass grafting

Key Question 1b. Over what period of time are the comparative benefits of PCI and CABG sustained?

Coronary revascularization with either PCI or CABG treats a limited number of localized obstructions within the vascular bed. However, coronary atherosclerosis is a diffuse and progressive disease process, so revascularization is inherently limited and does not "cure" the underlying disease. Revascularization does not replace the need for ongoing medical therapies, including antiplatelet agents, cholesterol reduction, smoking cessation, control of hypertension and diabetes, and lifestyle modification. Progressive coronary disease in untreated segments of the coronary arterial system, as well as late deterioration of vein grafts, surgical anastamoses, dilated segments, and implanted stents may lead to subsequent events. Long-term comparative results of PCI and CABG are important for assessing the durability of these techniques.

The follow-up reported in the RCTs ranged from six months to 13 years. Eleven trials (randomizing 7,412 patients, 77 percent of all patients enrolled in the trials) have reported two or more years of follow-up and ten trials (randomizing 6,314 patients, 65 percent of all patients enrolled) have reported five or more years of follow-up.

The PCI-CABG survival difference in these 11 trials was +0.1 percent at one year and -0.6 percent at five years (Figure 11). There is no solid evidence that the survival difference changed significantly between one year and five years. (An analysis of odds ratios provided a similar result.)

More extended follow-up of PCI and CABG trials would be desirable to establish whether the well-known tendency of saphenous vein grafts to deteriorate over time affects late comparative outcomes. Only four trials reported follow-up beyond five years (BARI, EAST, GABI, and RITA). The GABI study has reported the longest follow-up of any randomized trial and found the Kaplan-Meier survival curves crossed three times between two and seven years of follow-up, with the advantage for CABG over PCI between seven and ten years almost gone at 13 years. In the EAST trial, the small survival advantage for CABG at three years (0.9 percent) grew slightly at five years (3.3 percent) and remained essentially unchanged at eight years (3.4 percent). In the BARI trial, the CABG survival advantage was 3.0 percent at five years, 3.5 percent at seven years, and 2.5 percent at ten years.[85] In the RITA trial, the PCI-CABG survival difference was 0 percent at five years and 1.4 percent at seven years. These four trials with long-term follow-up show no consistent pattern in PCI-CABG survival difference after five years.

The advantage of CABG in relief of angina grew progressively smaller between one year (8.5 percent) and five years of follow-up (6.5 percent) (Figure 16). The few trials reporting longer follow-up suggest that the prevalence of angina continues to equalize over extended follow-up. It is uncertain whether recurrent angina results more from progression of underlying coronary disease or eventual failure of the initial treatment (i.e., restenosis, graft failure).

The quality of evidence demonstrating little change in the survival difference between CABG and PCI between five and eight years after initial treatment is *acceptable* because, although only four trials report data during this interval, they are large, well-designed RCTs. However, there is insufficient information after ten years to draw reliable conclusions about the comparative efficacy of PCI and CABG. None of the stent-era trials has reported follow-up beyond five years, and the late effects of stent implantation may differ from those of balloon angioplasty.

Key Question 2. Is there evidence that the comparative effectiveness of PCI and CABG varies based on:

a. Age, sex, race, or other demographic risk factors?
b. Coronary disease risk factors, diabetes, or other comorbid disease?
c. Angiographic-specific factors?
d. CABG-specific factors?
e. Clinical presentation?
f. Adjunctive medical therapies?
g. Process characteristics such as provider volume?
h. Prior PCI or CABG revascularization procedures?

Comparative Effectiveness by Age, Gender, and Race (2a)

Demographic factors such as age and sex are well-established prognostic factors in patients with coronary artery disease. Procedural, short-term risk of coronary revascularization is also affected by age and sex, with older patients and women experiencing more short-term adverse effects. The extent to which age, sex, and demographic factors affect the comparative outcomes of PCI and CABG has not, however, been clearly established.

Age

Outcomes by age were examined by the BARI, AWESOME, and stent trials. Overall, older patients had more procedural complications, especially stroke. In the BARI trial, patients aged 65 years and older had lower overall survival compared with younger patients. The survival difference between PCI and CABG at seven years was slightly greater for CABG in the older patients (-4.7 percent PCI-CABG survival difference; CABG survival 78.7 percent vs. PCI 74.0 percent) than younger patients (-2.8 percent PCI-CABG survival difference; CABG 88.1 percent vs. PCI 85.3 percent). Older patients had less recurrent angina, however, and fewer repeat revascularization procedures. The pooled results of four trials employing stents (ARTS, ERACI-II, MASS-II, SOS) found a lower one-year survival, freedom from MI, and freedom from stroke among patients aged 65 years or older compared with younger patients. However, there was no statistically significant survival difference PCI and CABG.

An important limitation of the randomized trial data is that very few patients over 75 years of age were enrolled. While a formal upper age limit was imposed by only a few trials, relatively few very old patients met eligibility criteria or were considered for enrollment. Consequently, no conclusions can be drawn about the comparative effectiveness of PCI and CABG in patients above 75 years of age.

Gender

Women were enrolled in essentially every RCT comparing PCI and CABG, so there is a substantial basis for applying trial results to both women and men. Outcomes according to gender were analyzed by BARI, SOS, and the pooled stent trials. In the BARI trial, women had lower overall survival, however only at seven years. The survival difference between PCI and CABG was similar, however, in women (-3.4 percent PCI-CABG survival difference: 82.6 percent CABG vs. 79.2 percent PCI) and in men (-3.5 percent PCI-CABG survival difference: 85.1 percent CABG vs. 81.6 percent PCI). In the SOS trial, women had lower quality of life at baseline, but improved after coronary revascularization. In men, quality of life scores improved more with CABG than with PCI, whereas in women the improvements were similar with CABG and PCI. In the pooled stent-trial data (ARTS, ERACI-II, MASS-II, SOS), women had slightly more events at one year, but relatively similar clinical outcomes as men.

Race

The vast majority of patients in the clinical trials were of European ancestry, so relatively few conclusions can be drawn regarding variation in outcomes according to race and ethnicity. Outcomes according to race were reported only by the BARI trial and registry. Overall, African-American patients had a 1.49 times lower risk of overall survival (CI: 1.07 to 2.08). There was no significant interaction between race and treatment assignment on outcome.

Summary (2a)

The evidence is robust that age and sex affect survival after both CABG and PCI. The evidence regarding the comparative effectiveness of PCI and CABG by age and gender is only *acceptable,* because relatively few RCTs reported these data and those that did showed no consistent effect of age or gender upon the comparative effectiveness of PCI and CABG. However, there is weak evidence regarding the effect of race on the comparative effectiveness of these procedures—a key gap in the literature.

Comparative Effectiveness for Patients With Diabetes (2b)

Patients with diabetes who have coronary disease have substantially higher morbidity and mortality than patients without diabetes who have coronary disease. The poor prognosis among patients with diabetes has been reported consistently in patients undergoing coronary revascularization procedures, and may be due to more extensive coronary disease at the time of revascularization, more rapid progression of coronary atherosclerosis in follow-up, or both. The relative efficacy of PCI and CABG in the high-risk population of patients with diabetes has been of particular interest.

The BARI trial examined in detail the outcomes of patients with diabetes. While this subgroup was not prespecified for analysis in the published BARI protocol, it was added by the Data and Safety Monitoring Board early in the trial. At five years, the 353 patients in BARI with treated diabetes randomized to CABG had significantly better survival (80.5 percent) than patients with treated diabetes randomized to PCI (65.5 percent). By contrast, patients without

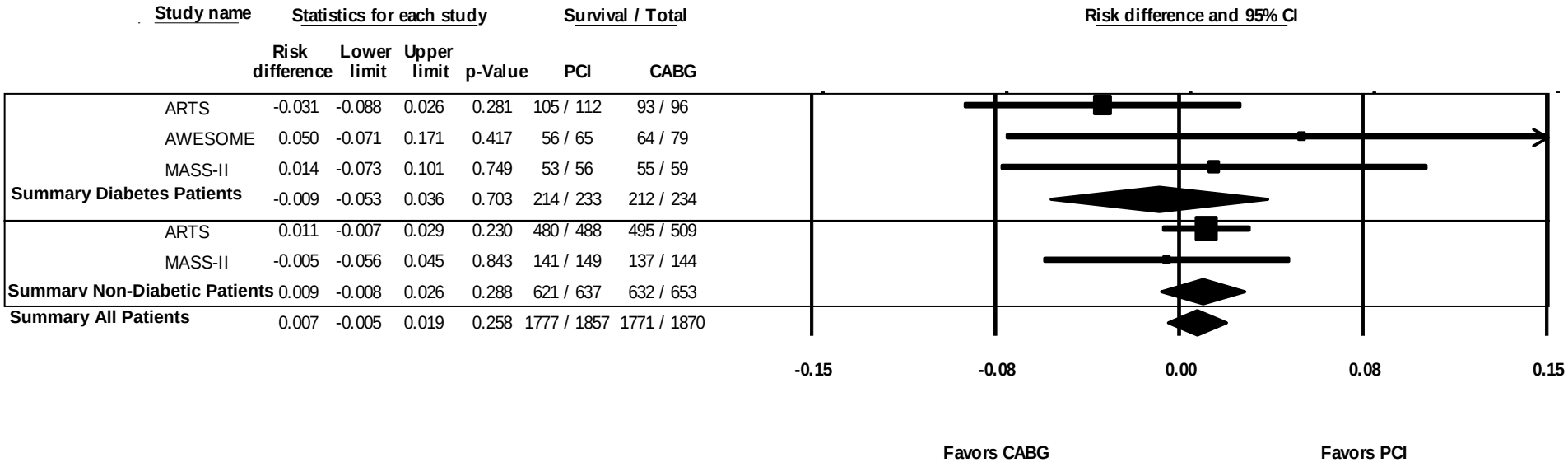
treated diabetes in BARI had equivalent survival at five years when assigned to PCI (91.1 percent) or CABG (91.1 percent).

The BARI findings prompted other randomized trials to examine their outcomes in patients with diabetes, including CABRI, EAST, and RITA-I among the early balloon angioplasty studies, and ARTS, AWESOME, ERACI-II, and MASS-II among the more recent trials that used coronary stents. Survival at one and five years was reported for six trials (Appendix C Table 7 and Figures 20 and 21). None of these studies reported as dramatic a difference in survival in patients with diabetes as BARI. In EAST, for example, the 59 patients with treated diabetes had slightly better survival in the PCI arm at three years, equivalent survival at five years, and slightly better survival in the CABG arm at eight years. In CABRI, the 124 patients with diabetes had twice the overall risk of patients without diabetes, with a four year survival of 87.5 percent among patients assigned to surgery and 78.4 percent among patients assigned to angioplasty (no p-value reported). Among the 62 patients with diabetes in the RITA trial, 27 of the 29 PCI patients survived compared with 25 of the 33 CABG patients at a median follow-up of 6.5 years (no p value reported). Several of the stent-era trials reported data on patients with diabetes, but the best analysis comes from the pooled individual patient data from the ARTS, ERACI-II, MASS-II, and SOS trials. At one year, patients with diabetes had one year survival difference of 2.1 percent (94.6 percent when assigned to PCI versus 96.5 percent when assigned to CABG), which was larger than the overall one year survival difference of 0.2 percent (PCI 97.0 percent, CABG 98.2 percent).

A quantitative analysis of the comparative outcomes of PCI and CABG in patients with diabetes shows no significant difference in survival at one year (Figure 20) or at five years (Figure 21). The summary PCI-CABG survival difference at five years was greater for CABG by only 0.8 percent, but with very wide confidence limits of -8.3 percent to 6.6 percent (PCI/CABG odds ratio 0.87; CI: 0.51 to 1.49).

The quality of the evidence comparing PCI with CABG in patients with diabetes is only *acceptable* given that it is neither consistent nor conclusive despite the number of trials that have examined this issue. The marked benefit of CABG reported by the BARI trial was not seen in other randomized trials, suggesting this result may be attributable to the play of chance. None of the other trials enrolled large numbers of patients with diabetes, however, and follow-up in the recent stent-era trials is too short to be conclusive. Pooling of the individual patient level data from all randomized trials would provide the most definitive analysis of outcomes in patients with diabetes. The ongoing FREEDOM trial (Future Revascularization Evaluation in patients with Diabetes: Optimal Management of multi-vessel disease, ID NCT00086450), Veterans Affairs CARDS Trial (Coronary Revascularization in Diabetes, ID NCT 00326196) and CARDia Trial (Coronary Artery Revascularization in Diabetes)[214] will provide data on outcomes in patients treated using drug-eluting stents and contemporary bypass surgery (Appendix C Table 14).

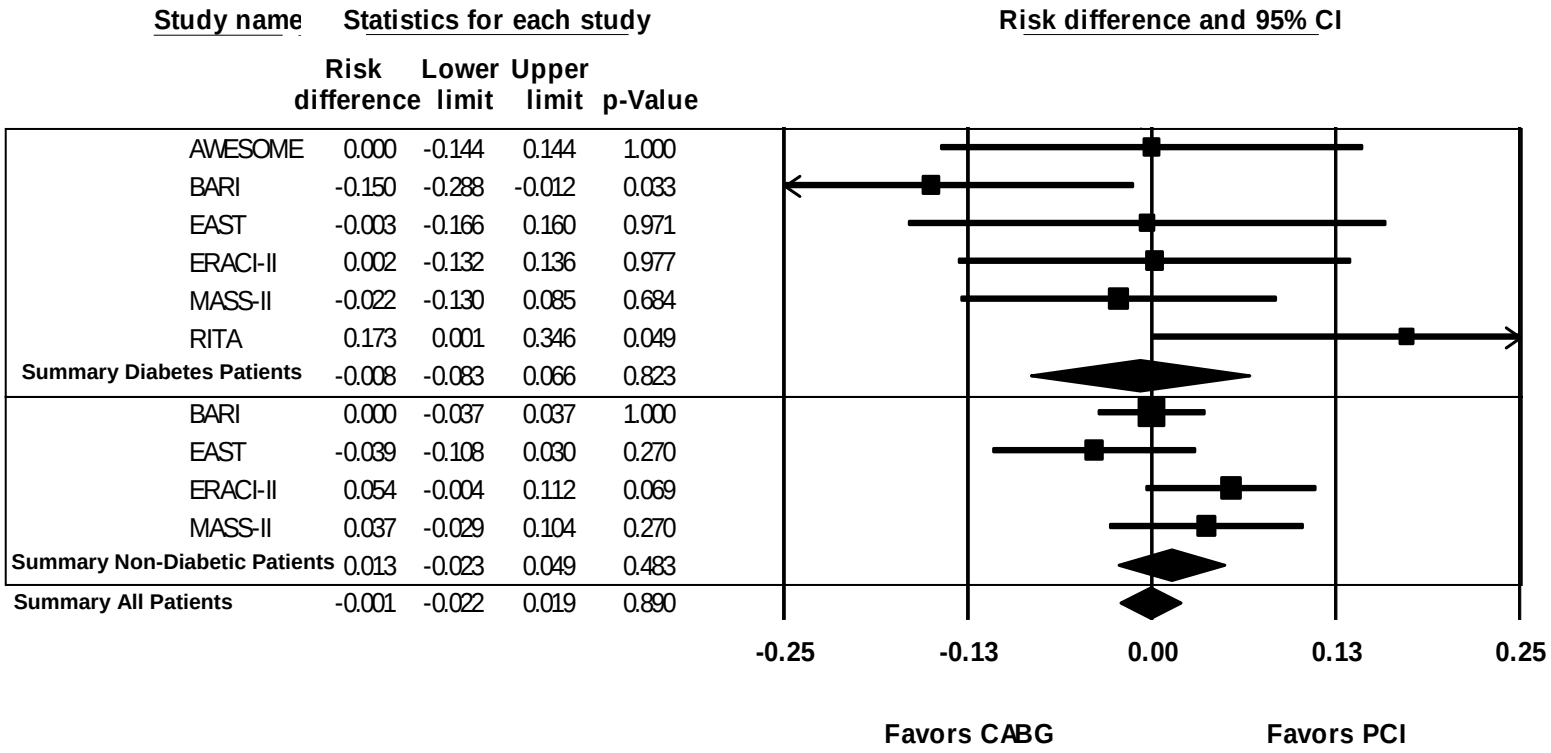
Figure 20. Comparison of survival among patients with and without diabetes at 1 year



Patients with diabetes: Heterogeneity statistics: Q=1.8 ; p-value = 0.4; I-squared =0. PCI/CABG Odds Ratio: 1.09 (CI: 0.55, 2.13; p=0.8)
Patients without diabetes: Heterogeneity statistics: Q=0.4 ; p-value = 0.5; I-squared =0. PCI/CABG Odds Ratio: 1.09 (CI: 0.55, 2.13; p= 0.4)

Note: All studies reporting comparative effectiveness data for patients with diabetes were included in this analysis, not just the studies reporting comparative outcomes for patients with and without diabetes. Hazard Ratios from the GABI trial for mortality following PCI or CABG were reported not to be different among patients with or without diabetes; however, these data were not shown.[108] PCI=percutaneous coronary intervention; CABG=coronary artery bypass grafting; CI=confidence interval

Figure 21. Comparison of survival among patients with and without diabetes at 5 years



Patients with diabetes: Heterogeneity statistics: Q=8.4 ; p-value = 0.14; I-squared =40. PCI/CABG Odds Ratio: 0.87 (CI: 0.51, 1.49; p=0.6)
Patients without diabetes: Heterogeneity statistics: Q=5.0 ; p-value = 0.2; I-squared =40. PCI/CABG Odds Ratio: 1.16 (CI: 0.75, 1.78; p=0.5)

Note: All studies reporting comparative effectiveness data for patients with diabetes were included in this analysis, not just the studies reporting comparative outcomes for patients with and without diabetes. Hazard Ratios from the GABI trial for mortality following PCI or CABG were reported not to be different among patients with or without diabetes; however, these data were not shown.[108] PCI=percutaneous coronary intervention; CABG=coronary artery bypass grafting; CI=confidence interval

Comparative Effectiveness for Patients With Other Coronary Disease Risk Factors (2b)

The major risk factors for the development of coronary artery disease include age, sex, diabetes, smoking, hyperlipidemia, hypertension, and family history of premature vascular disease. Other risk factors include obesity, chronic kidney disease, and the presence of atherosclerosis in other vascular beds. The effects of age, sex, and diabetes upon the comparative efficacy of PCI and CABG have been studied extensively and have already been discussed. The potential effects of the other cardiac risk factors have not been studied as often.

Tobacco use

Cigarette smoking is an established risk factor for the development of coronary disease, and continued smoking is an adverse prognostic factor after coronary events and coronary revascularization. Patients are strongly urged to stop smoking at the time of coronary revascularization. The effect of smoking upon outcome of PCI and CABG was examined only by the BARI trial and by the pooled stent trials (ARTS, ERACI-II, MASS-II, SOS). In the BARI study,[61] current smoking increased overall mortality with an adjusted relative risk of 1.72 (CI 1.28 to 2.32), and former smoking also increased overall mortality, with an adjusted odds ratio of 1.35 (CI 1.06 to 1.72). The interaction between smoking and treatment was not significant, indicating that current and former smoking increased risk to a similar extent in PCI- and CABG-assigned patients. In the pooled stent trial data,[17] smoking was not consistently associated with one-year mortality.

Hypertension

Hypertension is an established risk factor for cardiovascular morbidity and mortality. The BARI trial[61] found that hypertension increased total mortality, with an adjusted relative risk of 1.40 (CI: 1.14 to 1.72). There was no evidence of interaction with treatment assignment, suggesting that hypertension increased risk similarly in PCI-assigned and CABG-assigned patients.

Hyperlipidemia and family history

Hyperlipidemia and family history of coronary artery disease have not been studied in PCI-CABG RCTs to determine whether they affect subsequent outcome.

Obesity

Obesity is a risk factor for coronary artery disease, primarily through its effect on diabetes, hypertension, and hyperlipidemia. Obesity also increases the risk of cardiac procedures directly, as PCI and CABG can be more difficult to perform in obese patients. The ARTS trial and the BARI trial analyzed the effect of obesity on subsequent outcomes. In ARTS, only 28 percent of the patients had a normal body mass index (BMI) of less than 25 kg/m^2, while 50 percent were overweight (BMI 25 to 30), and 22 percent were obese (BMI >30). Overall survival in ARTS was not affected by BMI, nor were freedom from MI and stroke.[42] Repeat revascularization was

not related to BMI in patients assigned to PCI, but increased BMI was associated with fewer repeat procedures in patients assigned to CABG. ARTS did not analyze functional outcomes, such as angina or quality of life, according to BMI. In the combined BARI trial and registry of 3,634 patients,[72] 2 percent of patients had a low BMI (<20), 24 percent had a normal BMI (20-25), 46 percent were overweight (BMI of 25-30), 21 percent were obese (BMI 30-35), and 7 percent were morbidly obese (BMI>35). Obesity in the BARI data was strongly associated with diabetes and hypertension, and inversely with age and smoking. All cause survival was decreased in those with either a BMI <20 or a BMI ≥35, with the relationship attenuated somewhat by adjustment for other prognostic factors. Survival decreased steadily as BMI increased in CABG-assigned patients, but not in PCI-assigned patients. Consequently, the differences in five-year crude survival rates between CABG-assigned and PCI-assigned patients diminished with increasing weight: for BMI <20 the five-year PCI-CABG survival difference was -12.5 percent, for BMI of 20-25 it was -4.6 percent, for BMI 25-30 it was -0.5 percent, for BMI 30-35 it was 0 percent, and for BMI ≥35 it was +1.4 percent (i.e., PCI-assigned patients had higher survival). This analysis was not, however, adjusted for potential confounding factors such as age, gender, or diabetes.

Renal dysfunction

Renal dysfunction is increasingly recognized as a cardiac risk factor. While patients with end-stage renal disease and severely compromised renal function were generally excluded from trials of PCI and CABG, the effects of modestly abnormal renal function upon outcome have been analyzed by the BARI trial[84] and the ARTS trial.[43] Patients in ARTS with estimated creatinine clearance of ≤ 60 ml/min were defined as having chronic kidney disease.[43] The 25 percent of the ARTS population with chronic kidney disease had a significantly higher risk of death, MI, stroke, and transient ischemic attack, with a relative risk of 1.9 (CI: 1.4 to 2.7). There was no difference in the ARTS trial between PCI and CABG in this outcome over three years of follow-up (PCI/CABG hazard ratio 0.93), nor of overall mortality (PCI/CABG hazard ratio 0.98). In the combined BARI trial and registry,[84] only 2.1 percent of patients had chronic kidney disease, defined as a serum creatinine above 1.5 mg/dL. Chronic kidney disease was associated with increased procedural risk and with long-term (seven year) mortality, with a relative risk of 2.3 (CI: 1.6 to 3.3). The interaction with treatment assignment was not significant, however, implying that risk was increased by chronic kidney disease to a similar extent in PCI- and CABG-assigned patients.

Vascular disease

Atherosclerosis in other arterial beds, including the cerebrovascular and peripheral vascular systems, is generally associated with more extensive coronary atherosclerosis and worse prognosis. Only the BARI trial examined the outcomes of patients with concomitant vascular disease.[83] Peripheral vascular disease decreased five-year survival in the combined BARI trial and registry population, with a relative risk of 1.50 (CI: 1.20 to 1.88). There was no significant interaction with treatment assignment, however. In the BARI trial population the presence of clinically evident disease in either the peripheral vascular system (claudication, peripheral vascular surgery or abdominal aortic aneurysm) or in the cerebrovascular system (prior stroke, transient ischemic attack, carotid surgery, carotid bruit, or documented carotid disease) was

present in 17 percent of the trial population. Overall five year survival was substantially worse in patients with evident non-coronary atherosclerosis (75.8 percent versus 90.2 percent $p<0.001$). Five-year survival was better by 8.9 percent in CABG-assigned patients with vascular disease (80.3 percent vs. 71.4 percent, $p=0.11$), which was greater than the PCI-CABG survival difference of -3.0 percent in the overall BARI trial. Angina was more frequent in follow-up among patients with non-coronary atherosclerosis.

Summary (2b)

The quality of evidence regarding the comparative effectiveness of patients with coronary disease risk factors other than diabetes is generally *weak* given the paucity of consistent, RCT data.

Comparative Effectiveness by Extent of Coronary Artery Disease (2c)

Coronary revascularization procedures treat obstructive coronary artery disease in any of the three major epicardial coronary artery systems: the left anterior descending (LAD), the left circumflex, and the right coronary artery. The mechanism of action of coronary revascularization suggests a dose-response relationship between the number of vessels treated and the therapeutic benefit of revascularization; comparisons of CABG with medical therapy show the survival benefit conferred by CABG increases directly with extent of disease.[158] It would be reasonable to expect that the difference in outcome between PCI and CABG might depend upon the extent of disease.

Previously, we presented the comparison of survival difference between PCI and CABG for single- versus multi-vessel disease trials (Figure 12). When compared across all trials, we found no significant survival difference between the procedures. However, a within-trial comparison of outcomes according to the extent of disease is the best test of a possible "dose-response" relationship, since the sources of variation are reduced when revascularization is done within the same centers and after applications of the same inclusion and exclusion criteria. Most studies did not, however, report outcomes separately for patients with one-, two-, and three-vessel disease. The BARI trial found overall better survival among the 1,024 patients with two-vessel disease than the 750 patients with three-vessel disease. The survival difference between PCI and CABG at five years was greater in patients with three-vessel disease (-3.9 percent PCI-CABG survival difference: 84.7 percent PCI vs. 88.6 percent CABG) than in patients with two-vessel disease (-2.1 percent PCI-CABG survival difference; 87.6 percent PCI vs. 89.7 percent CABG) (Table 14). The smaller EAST trial also reported a larger CABG-PCI survival difference among patients with three-vessel disease than patients with two-vessel disease. A similar trend was reported in the pooled data from four stent-era trials (ARTS, ERACI-II, MASS-II, SOS). By contrast, the RITA-I study found very little difference in survival between the 455 patients with single-vessel disease and the 556 patients with multi-vessel disease (mostly two-vessel disease) and similar PCI-CABG survival differences at a median 6.5 years of follow-up.

As previously discussed, clinical registry studies show a significant interaction between extent of coronary artery disease and the PCI/CABG hazard ratio for long-term survival. The Duke data, for instance, show a graded relationship for PCI/CABG hazard across a scale with nine categories of extent of disease.[156, 159] Other clinical registries show a similar relationship between extent of disease and the relative efficacy of CABG and PCI.

Overall, these data suggest that mortality in patients with three-vessel disease may be reduced somewhat more by CABG than by PCI and that in one-vessel disease there is little mortality difference between PCI and CABG. A more definitive analysis would require pooling individual patient level data from randomized trials that enrolled patients with different extent of coronary disease.

The quality of evidence specifically addressing the comparative effectiveness of PCI and CABG is *acceptable* for two-vessel versus three-vessel disease, with consistent results from within several trials and confirmed by evidence from clinical registries. The quality of evidence regarding single-vessel LAD versus multi-vessel disease is also *acceptable.*

Table 14. Survival for patients according to the extent of coronary artery disease

Trial Name	Anatomy	PCI			CABG		
		N randomized	N alive at 5 years	5 year survival (%)	N randomized	N alive at 5 years	5 year survival (%)
RITA	SVD	233		92.7	222		90.5
	MVD	277		92.1	279		91.4
BARI	2 vessel disease	521		87.6	521		89.7
	3 vessel disease	375		84.7	375		88.6
EAST	2 vessel disease	119	108	90.8	117	106	90.6
	3 vessel disease	79	66	83.5	77	71	92.2
ERACI-II	2 vessel disease					94	89.4
	3 vessel disease					131	87.8

PCI=percutaneous coronary intervention; CABG=coronary artery bypass grafting; SVD=single-vessel disease; MVD=multi-vessel disease

Comparative Effectiveness for Patients With Low Left Ventricular (LV) Function (2c)

Left ventricular (LV) function is generally accepted to be one of the strongest prognostic factors in patients with coronary artery disease. A clear association between decreased LV ejection fraction (EF) and survival has been repeatedly demonstrated in numerous studies enrolling various patient populations. Coronary revascularization increases survival compared with medical therapy to a greater extent in absolute terms in patients with reduced EF compared with patients with normal EF, even though the degree of relative risk reduction is similar in these populations.[158] This reflects the principle that higher risk populations benefit more than low risk populations when a therapy provides a consistent relative reduction.

Most trials comparing PCI and CABG enrolled patients with relatively preserved LV function (Appendix Table 2) and a low prevalence of heart failure. The limited range of ejection fractions within the trials may not permit a stringent test of whether the comparative effectiveness of PCI and CABG varies with LV function. Only the BARI trial[63, 68] and the AWESOME trial[56] reported specific analyses of LV function. Overall five year survival in the BARI trial was worse in the 22 percent of patients with reduced LV function than in patients with normal LV function.[58] The PCI-CABG survival difference at five years was 0.4 percent in the patients with reduced LV function (CABG 80.7 percent, PCI 81.1 percent), whereas it was -4 percent in patients with normal LV function. At seven years, the PCI-CABG survival differences were -1.3 percent for the abnormal and -3.6 percent for the normal LV function groups. A similar pattern was seen in BARI randomized patients with a history of congestive heart failure, in whom the seven year CABG-PCI survival difference was 4.3 percent compared

with 3.4 percent in patients without heart failure. The AWESOME trial enrolled a very high risk population of patients with refractory angina and increased risk for CABG, 20 percent of whom had an EF <35 percent. The patients with low EF had worse overall survival at three years, with a slight advantage of 3 percent in the CABG-assigned patients (CABG survival 72 percent, PCI survival 69 percent), while in the overall trial population PCI-assigned patients had a slightly better survival (PCI-CABG survival difference 1 percent, CABG survival 79 percent, PCI survival 80 percent). Overall, the small and inconsistent differences seen in the trials provide no convincing evidence of variation in the comparative efficacy for PCI and CABG by the level of LV function.

The quality of the evidence regarding the comparative effectiveness of PCI and CABG according to LV function was *weak*.

Comparative Effectiveness by PCI-Specific Factors (2c)

Eleven trials used bare metal stents, 11 used balloon angioplasty, and only the Seoul-Hong trial used drug-eluting stents (Table 4). As discussed above, comparing the more recent stent trials to the earlier balloon trials, we found a smaller survival difference between PCI and CABG; however, this survival difference between PCI and CABG did not differ statistically from zero for either PCI procedure (Figures 13 and 14).

The quality of the evidence regarding the comparative effectiveness of various PCI techniques on key comparative outcomes of PCI versus CABG was *acceptable*.

Comparative Effectiveness by CABG-Specific Factors (2d)

The technique of conventional coronary bypass surgery includes a median sternotomy, cardiopulmonary bypass, and use of venous or arterial grafts. There are numerous technical variations upon this basic CABG technique, with inter-institutional and inter-operator variability. There are also secular trends in the technical approach, primarily an increased emphasis on the use of internal mammary grafts, which have much better long-term patency than saphenous vein grafts.

There has been considerable interest recently in coronary surgery that avoids either a median sternotomy or cardiopulmonary bypass or both. "Minimally invasive" surgery (MIDCAB), which is performed through a small throracotomy incision on a beating heart, has been compared with PCI in several small randomized trials: including the AMIST, Groningen, Leipzig, Octostent, Poland, Seoul-Kim, Seoul-Hong, and SIMA studies. These studies enrolled patients with single-vessel proximal LAD disease (predominantly or exclusively) and generally used PCI with stents as the comparator. These trials showed similar outcomes over a relatively short follow-up period. There are only a few early trials of balloon angioplasty and standard CABG (Lausanne, MASS-I) in patients with single-vessel disease whose results can be compared with these trials. In general, the survival differences over one to two years of follow-up are comparable (Figure 9).

Standard CABG was used in all trials that enrolled patients with multi-vessel disease. There was some variability in the use of left internal mammary (IMA) grafting among these trials, ranging from a low of 37 percent in the early GABI study to over 90 percent in the more recent ARTS, MASS-II, and SoS studies. The PCI-CABG survival differences at one year are plotted in Figure 22 against the percentage of surgical patients who received an IMA graft. We

performed a regression weighted by the sample size of the RCT and found that as the percentage of IMA grafts increases, there is a trend toward higher survival in CABG-assigned patients at 1-year but not at 5-years (neither association was statistically significant). There was a much weaker association between use of IMA graft and survival at 5-years (Figure 23).

Figure 22. Association between survival at 1-year and use of mammary artery grafts

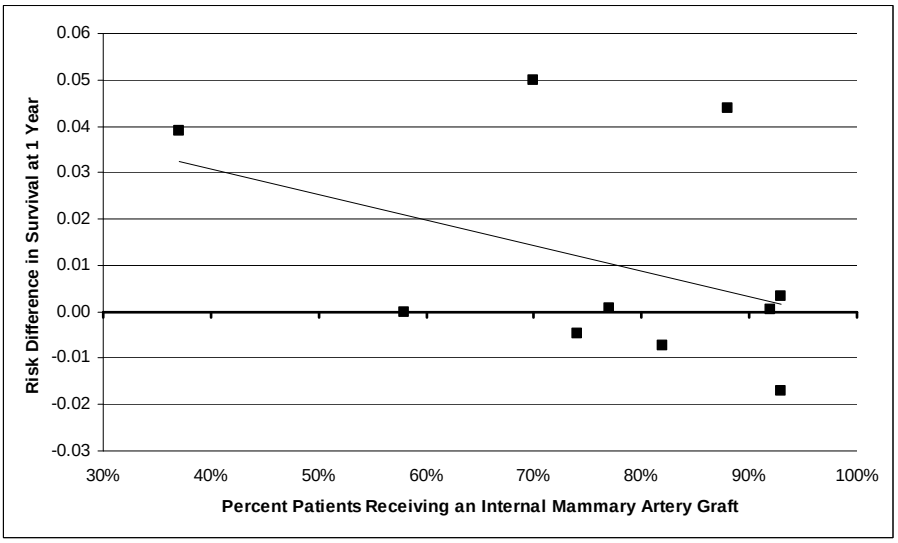
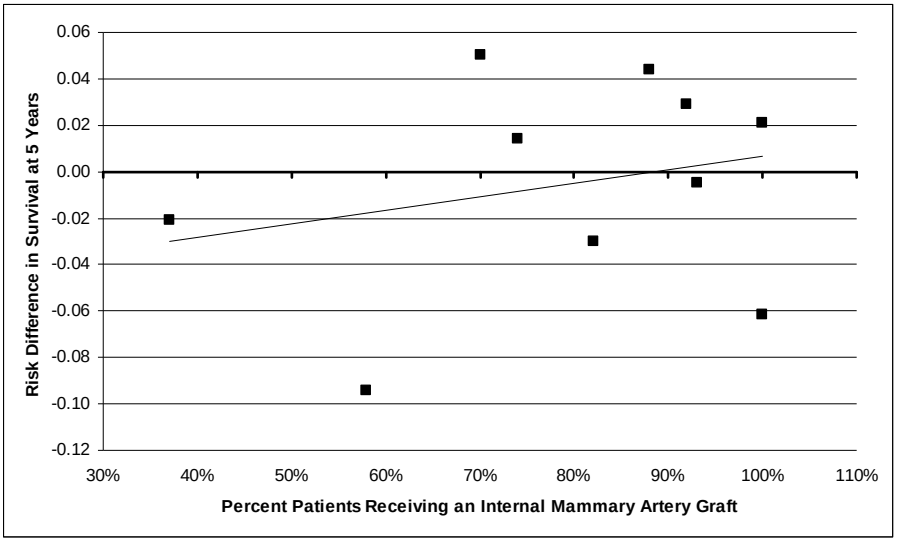


Figure 23. Association between survival at 5-years and use of mammary artery grafts



The randomized trials did not report in any detail the use of normothermic versus hypothermic cardiopulmonary bypass, the use of specific types of cardioplegia, or details of saphenous vein harvesting and handling. The PCI-CABG trials therefore provide little direct evidence about the potential effects of these variations in CABG technique upon the comparative effectiveness of CABG and PCI. It is beyond the scope of this report to review trials that randomized patients receiving CABG to different technical approaches. A recent meta-analysis concluded that blood cardioplegia provided superior myocardial protection as compared with

crystalloid cardioplegia, based on a review of 34 randomized trials.[215] Off-pump CABG has been shown to have fewer short-term complications than conventional on-pump CABG in several meta-analyses; long-term clinical follow-up has not yet been reported, however.

No RCTs comparing PCI and CABG have used transmyocardial revascularization. A recent meta-analysis of seven trials suggested that transmyocardial revascularization improved angina, but not survival.[216]

Given these gaps in the literature, the quality of the evidence regarding the comparative effectiveness of various CABG techniques on key comparative outcomes of PCI versus CABG was *weak*.

Comparative Effectiveness for Patients With Stable Angina Versus Unstable Angina (2e)

Patients with unstable angina or acute myocardial infarction have decreased short-term survival and increased serious morbidity compared with patients with stable forms of coronary artery disease. The procedural risks of coronary revascularization procedures are also increased in patients with acute coronary syndromes. It is uncertain whether procedural risks are increased to a similar extent by PCI and CABG, however.

While patients with acute coronary syndromes were enrolled in most trials (Appendix C Table 2), only three randomized trials examined in any detail the clinical outcomes of patients according to their clinical presentation: the ARTS trial,[41] the BARI trial [58, 61] and the SOS trial.[139, 144] In ARTS, 63 percent of the 1,205 patients had stable angina, while the remaining 37 percent had unstable angina as the qualifying clinical symptoms. At one-year of follow-up, the PCI-CABG difference in freedom from death, MI, and stroke was -2.2 percent among stable patients (CABG 92.6 percent, PCI 90.4 percent), versus 2.3 percent among unstable patients (CABG 88.9 percent, PCI 91.2 percent). More CABG patients than PCI patients were free of angina at one year: 13 percent more in stable angina (90 percent CABG, 77 percent PCI), and 6 percent more in unstable angina (89 percent CABG, 83 percent PCI). None of these differences were statistically significant. In the BARI trial, roughly two-thirds of patients had acute coronary syndrome, and one-third had stable angina. At five years of follow-up, the survival differences between CABG and PCI were similar in these subgroups: 2.7 percent in acute coronary syndromes (88.8 percent CABG, 86.1 percent PCI), versus 5.5 percent in stable angina (91 percent CABG, 85.5 percent PCI). In SOS, only 24 percent of patients had unstable angina, and they had relatively similar clinical outcomes at one year as patients with stable angina. Survival or freedom from Q-wave MI was slightly lower among PCI patients who had either unstable symptoms (0.4 percent) or stable angina (1.3 percent), and both groups had improved scores on the Seattle Angina Questionnaire.

The evidence from these three studies is that the comparative effectiveness of PCI and CABG is not greatly affected by the mode of clinical presentation. This statement should be qualified by noting that few patients were experiencing severe clinical instability at the time of randomization. Given the consistency of these results, we rated the evidence addressing this key question as *acceptable*.

Comparative Effectiveness by Adjunctive Medical Therapies (2f)

Adjunctive medical therapies may improve the safety and efficacy of coronary revascularization procedures. There have been multiple studies examining the efficacy of intravenous glycoprotein IIb/IIIa inhibitors, anticoagulation (heparin, low molecular weight heparin, etc.), and antiplatelet agents (clopidogrel, ticlopidine) in the setting of coronary angioplasty. A review of this extensive literature is beyond the scope of the present evidence report, since these studies did not compare PCI with CABG, only two alternative methods of PCI.[217]

Use of adjunctive medical therapy for PCI has been closely related to the increased use of coronary stents, because of concerns about stent thrombosis. Prolonged antiplatelet therapy has become standard after PCI, initially using aspirin and ticlopidine, and more recently using aspirin and clopidogrel. Anti-platelet therapy may reduce coronary events independent of any effect on the site of PCI, however, and may contribute to improved long-term outcomes in PCI-treated patients. Anti-platelet therapy is also recommended for patients after CABG, and so the comparative effectiveness of PCI and CABG would not necessarily be affected.

A subsidiary issue is whether patients who have undergone CABG are as likely as patients who have undergone PCI to comply with recommendations to use aspirin, beta-blockers, ACE-inhibitors, and statins. To the extent that evidence-based therapies are used differentially after PCI and CABG, long-term outcomes may be affected. There is relatively little evidence on this question, and patients in randomized trials may be more likely to comply with recommended therapies than the average patient who has had coronary revascularization. Recent data from the Duke Database shows relatively similar use medical of therapies after PCI and CABG.[218]

Given that the randomized trials did not provide comparative effectiveness data on the use of adjunctive medical therapy for PCI or CABG, we rated the quality of the evidence to answer this question *weak*.

Comparative Effectiveness by Hospital and Provider Volume (2g)

Randomized trials have not directly tested for differences in clinical outcomes of PCI and CABG on the basis of process characteristics. However, observational studies from administrative and clinical data sets have examined the relationship between procedure volume and short-term outcomes, both at the hospital level and the physician level.

Over the past several decades, a robust body of evidence has been developed demonstrating an inverse relationship between procedure volume and short-term adverse outcomes (primarily mortality) for numerous surgical procedures.[219, 220] These observations have led to recommendations that many procedures should be performed in "centers of excellence" meeting minimum standards for procedure volumes and outcomes.[221, 222] These volume-based referral recommendations[c] are controversial because of concerns about applying aggregate data to individual hospitals and individual practitioners; in reducing a continuous, non-linear relationship between volume and outcome to a binary "high/low" classification; and by

[c] Leapfrog's hospital annual procedural volume thresholds are currently 450 for CABG and 400 for PCI.[222] The ACC/AHA 2004 Guidelines suggest "a posture of close monitoring of institutions or individuals that perform less than 100 cases annually."[150] The AHRQ Guidelines Clearinghouse presents "Level B" evidence from the 2005 ACC/AHA/SCAI guideline that "elective PCI should be performed by operators with acceptable annual volume (at least 75 procedures) at high-volume centers (more than 400 procedures)," along with additional contingencies for lower volume operators and institutions.[148, 149]

considering procedure volume a good surrogate marker for outcome.[223-226] There are also several methodologic issues about the appropriate statistical approaches to test for the effects of volume upon outcome.[219, 220] In this section, we summarize the evidence available to date for CABG and PCI.

Systematic reviews

We identified four formal systematic reviews that examined the relationship between hospital or physician volume of coronary revascularization procedures and patient outcomes (Appendix C Tables 8 and 9). Two reviews focused exclusively on CABG,[22, 23] and the other two reviews analyzed both PCI and CABG (as well as other procedures).[219, 221]

Sowden and colleagues conducted a systematic review of U.S.-based studies of CABG hospital volume-outcome relationships, based on data from 1972 to 1992.[23] Of the eight unique studies, seven reported significantly or nearly significant reduced mortality with increasing hospital CABG volume, with the adjusted odds ratios for mortality in high versus low volume hospitals ranging from 0.44 (CI: 0.29 to 0.65) to 0.84 (CI: 0.66 to 1.07), at thresholds close to 200 cases per year (varied from 150 to 215 depending upon the study). They also observed case mix adjustment and time period effects, though could not distinguish the relative importance of each with the small number of studies.

A subsequent review by Kalant and Shrier identified 28 independent patient cohorts receiving CABG between 1972 and 1999. Based on 16 cohorts with volume as a categorical variable (above and below 200 procedures a year), the authors plotted odds ratios for perioperative survival (adjusted to varying degrees) by year of publication, and showed that 1) most cohorts evaluated (13 of 16) showed higher survival in the higher volume hospitals, and 2) the relationship between volume and outcome was not as strong in the cohorts from more recent years.[22] Five of the nine cohorts demonstrated an inverse association between surgeon volume and outcomes, but all five cohorts were from New York State.

Dudley and colleagues reviewed volume-outcome studies for a broad range of procedures, including 11 studies of CABG and six studies of PCI.[221] Almost all studies reported statistically significantly better outcomes in high volume hospitals, including nine of 11 CABG studies and all six PCI studies.

Halm and associates found that five of nine studies reported a significant association between volume and outcome based on PCI procedures performed between 1989 and 1997, and that six of eight CABG studies reported a significant association based on procedures performed between 1980 and 1995.[219] The absolute in-hospital survival rate difference (unadjusted) for high volume PCI hospitals versus low volume PCI hospitals had a median of 0.2 percent (range 0.0 percent to 1.4 percent), across studies, while the median difference between high and low volume CABG hospitals was 1.6 percent (range 0 percent to 4.4 percent). Studies of the relationship between physician volume and outcome were less uniform, with only one of five included PCI studies showing a significant association, whereas all three studies of individual surgeon volume and CABG outcome showed a significant association.

The previous reviews of volume-outcome associations generally pre-dated the introduction of coronary stents for angioplasty and of minimally invasive techniques for CABG. In addition, the previous reviews cover PCI less comprehensively than CABG. We therefore identified and extracted basic findings from 29 PCI volume-outcome studies (Appendix C Tables 10 and 11) conducted using large administrative or clinical registries (greater than 2500 patients), and

targeted our data extraction to 12 CABG studies published since the Kalant review (Appendix C Table 12). Some of these studies evaluated volume as a continuous variable, but most categorized hospitals or physicians into specific volume ranges with varying distributions from lopsided to completely even splitting among categories (Appendix C Table 13). We describe recent studies of the association between volume and outcome to explore whether the relationships established for earlier coronary revascularization methods continue to apply to more recently developed techniques.

Hannan and associates reviewed the outcomes of 107,713 PCI procedures performed in 34 hospitals in New York State between 1998 and 2000. Hospitals performing less than 400 procedures per year had roughly twice the rate of death and of death or same-day CABG, as higher volume hospitals. McGrath and coworkers also found a significant inverse relationship between volume and PCI procedural risk in their analysis of 167,208 Medicare patients treated in 1,003 hospitals during 1997.[182] Burton and colleagues found no relationship between hospital volume and procedural survival in their analysis of all 17,417 PCI procedures performed in Scotland between 1997 and 2003, but their study included only six hospitals[207] and did show a significant effect of hospital volume on the rate of emergency CABG.

All but one of the recent CABG volume-outcomes studies found a significant relationship between increased hospital volume and higher risk-adjusted short-term survival, though several have pointed to potential subgroups in which the relationship does not persist (Appendix C Table 12). The recent study by Welke evaluated Medicare patients from 1996 through 2001, and found that hospital volume was a poor discriminator of survival given the large ranges of risk-adjusted mortality among hospitals in each quintile examined. The few recent CABG studies that reported on associations between surgeon volume and outcomes reported a significant association as well.

Three recent studies[227,212, 228] examined both PCI and CABG outcomes according to hospital volume in large administrative datasets that included procedure outcomes between 1998 and 2001 (Table 14). The two studies that used thresholds of 450 CABG procedures and 400 PCI procedures to define high versus low volume hospitals reported statistically significant relationships between volume and outcome in separate analyses of the same national data set (Table 14). In contrast, the single study that used thresholds of 300 CABG procedures and 600 PCI procedures to define high and low volume hospitals found a significant relationship for CABG but not for PCI. The summary data from all three studies (Figure 24) suggest that the volume-outcome relationship is stronger when lower thresholds are used to classify hospitals.

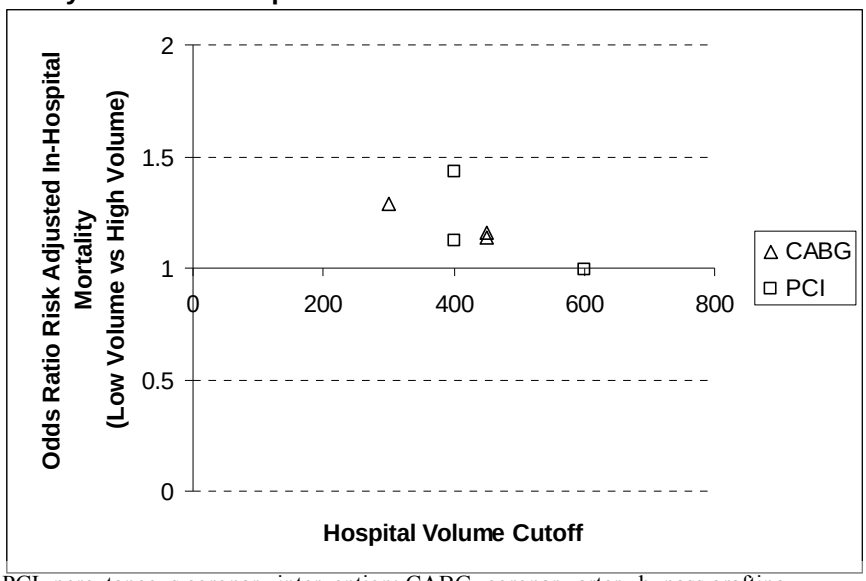
Overall, recent studies that included large numbers of procedures performed at a large number of hospitals have confirmed the relationship between increased volume and PCI procedural survival persists even with the availability of coronary stents. Similarly, higher hospital and physician CABG procedural volumes are generally associated with better outcomes in recent studies. The evidence is *robust* that CABG and PCI hospital volume are associated with short-term procedural risk in a number of circumstances. Nevertheless, the direction of the association is unknown for revascularization – whether "practice makes perfect" (poor outcomes are caused by less experience of lower volume environments) or whether "selective referral" (increasing volume in settings known to have good outcomes) or perhaps both are explanations of the association.

Table 15. Comparative effectiveness by volume-outcome

Citation	Population	Year	# Patients	Type of Data	Hosp Vol Levels	Hospital Vol & Risk-adjusted Mortality	Volume Distribution
Birkmeyer J et al.[227]	HCUP Nationwide Inpatient Sample	2000 only	394,165 (CABG) 678,296 (PCI)	Admin	CABG: <450, 450+/yr PCI: <400, 400+/yr	3.3% for less than 450 to 2.9% for 450 or more CABG cases (p<0.05); 2.0% to 1.4% for PCI below cutoff versus at or above 400 cutoff (p<0.05) [Odds Ratios and 95% CI not reported, but calculated OR for CABG: 1.14; for PCI: 1.43]	CABG: 39% patients at low volume; PCI: 14% at low volume (# of hospitals not provided)
Carey JS et al.[212]	Discharge abstracts from the California Office of Statewide Health Planning	1999-2001	82,353 (CABG) 153,755 (PCI)	Admin	CABG: <300, 300+/yr PCI: <600, 600+/yr	3.22% for less than 300 CABG cases versus 2.58% for 300 or more CABG cases (OR: 1.29 [CI: 1.19-1.41], p=0.0001); 1.39% to 1.41% for PCI below cutoff versus at or above 600 cutoff (not statistically significantly different for risk adjusted rates)	CABG: 95 low volume hospitals, 26 high volume; PCI: 116 low volume, 22 high volume (# of patients by category not provided)
Epstein AJ et al.[228]	HCUP Nationwide Inpatient Sample	1998-2001	1,496,937 (CABG) 2,500,796 (PCI)	Admin	CABG: <450, 450+/yr PCI: <400, 400+/yr	CABG: OR 1.16 (1.10-1.24) for low volume vs. high volume [p=0.001]. PCI: OR 1.12 (1.05-1.20) for low volume vs. high volume [p=0.001].	CABG: 38.4% patients treated at low volume; PCI: 14% patients treated at low volume (# of hospitals not provided)

Vol=volume; PCI=percutaneous coronary intervention; CABG=coronary artery bypass grafting; HCUP=Healthcare cost and utilization project; OR=odds ratio; CI=confidence interval; n/a: not available

Figure 24. Summary data from comparative effectiveness studies



PCI=percutaneous coronary intervention; CABG=coronary artery bypass grafting

Comparative Effectiveness by Prior Revascularization Procedures (2h)

The procedural risk of a second ("re-do") CABG operation is considerably higher than that of an initial CABG procedure. This excess risk may be related to the technical difficulties of operating in the presence of scar tissue from the first CABG. By contrast, second PCI procedures are generally regarded as having similar risk as initial PCI procedures, especially if performed to treat re-stenosis. Most studies have included patients with prior balloon angioplasty rather than prior coronary stenting, however, so the potential for increased risk of a second PCI in the area of an implanted stent has not been adequately studied.

One randomized trial and several clinical registries have compared PCI with re-do CABG in patients with a prior CABG (Table 15). In the AWESOME trial 142 patients with prior CABG were randomized to either re-do CABG (75 patients) or PCI (67 patients). While procedural survival was considerably higher in the patients assigned to PCI (100 percent vs. 92 percent), three-year survival was only slightly higher (78 percent vs. 73 percent) and not significantly different. In the large clinical registry studies from Cleveland, Emory, and Kansas City, patients with re-do CABG generally had more extensive coronary disease and a longer interval from initial CABG than patients treated with PCI (Table 15). Procedural mortality was higher for re-do CABG, but survival at five to six years of follow-up did not differ significantly.

The evidence is therefore *weak* that re-do CABG carries a higher procedural risk, but there is no clear evidence that long-term outcomes differ significantly.

Table 16. Studies of patients with prior revascularization procedures

Study	Years	Procedure	# Pts	Age	Male	Prior MI	DM	Years p CABG	3-VD	LVEF	Proc Survival %	Proc Q wave MI	F/U Years	Survival	Survival Comparison
Kansas City[169]	1987-1988	PTCA	468	62.2	83%	56%	19%	6.6	77%	46%	99.6	0.9%	6	74%	
Kansas City[169]	1987-1989	re-CABG	164	63.6	85%	42%	21%	8.9	74%	48%	92.7	6.1%	6	73%	p=0.32
Emory[166]	1980-1994	PTCA	2613	61	80%	56%	22%	6.1	56%	53%	98.8	1.4%	5	78%	
Emory[166]	1980-1995	re-CABG	1561	61	84%	20%	22%	7.9	75%	51%	93.2	5.4%	5	76%	Hazard Ratio CABG/PCI 1.01 after adjustment (insignificant)
Cleveland[154]	1995-2000	PTCA	704	66	79%	57%	34%	8.2	83%	48%	98.3	0.3%	5	75%	
Cleveland[154]	1995-2001	re-CABG	1487	65	84%	19%	33%	11.8	88%	44%	97.2	1.4%	5	80%	Hazard Ratio PCI/CABG 1.27 (1.07-1.51) unadjusted, 1.47 (0.94-2.28) after adjustment
AWESOME RCT[52]	1995-2000	PTCA	67	39% > 70		28%		65%	16% < 35	100.0		3	76%		
AWESOME RCT[52]	1995-2001	re-CABG	75	40% > 70		44%		70%	15% < 35	92.0		3	73%	Not significant	
AWESOME Pt-Choice Registry[52]	1995-2002	PTCA	74	45% > 70		38%		62%	8% < 35	100.0		3	86%		
AWESOME Pt-Choice Registry[52]	1995-2003	re-CABG	32	47% > 70		20%		62%	25% < 35	84.0		3	65%	p< 0.05 in patient choice	
AWESOME MD-Directed[52]	1995-2004	PTCA	357	38% > 70		35%		58%	17% < 35	99.4		3	77%		
AWESOME MD-Directed[52]	1995-2005	re-CABG	155	36% > 70		28%		71%	11% < 35	91.6		3	71%	Not significant	

Pts=patients; MI=myocardial infarction; DM=diabetes; VD=vessel disease; Year p CABG=years prior coronary artery bypass graft; LVEF=left ventricular ejection fraction; Proc Mort=procedural mortality; Proc Q-wave MI=procedural Q-wave myocardial infarction; F/U=follow-up; RCT=randomized controlled trial; PTCA=percutaneous transluminal coronary angioplasty; CABG=coronary artery bypass grafting; MD=physician

Summary and Discussion

The comparative effectiveness of PCI and CABG for patients with the middle spectrum of coronary artery disease who are eligible for both procedures has been assessed in 23 randomized trials that enrolled 9,963 patients, as well as in several large clinical registries. These published studies provide a robust body of evidence regarding the overall outcomes of these alternative coronary revascularization procedures (Figure 25). Despite this solid evidence for overall comparative effectiveness, there is much less evidence regarding the potential for variations in clinical outcomes according to patient-specific and provider-specific characteristics. Most clinical trials have not reported outcomes in key subgroups. Outcomes in the most intensively studied subgroup, patients with diabetes, have been reported by only seven of the 23 trials; outcomes according to other key coronary risk factors have been reported less frequently. Nevertheless, some conclusions can be drawn on the basis of the published trial and registry results.

Outcomes Overall

Procedural survival was high for both PCI and for CABG in the randomized trials and did not differ significantly (PCI-CABG procedural survival difference of 0.1 percent). Procedural survival in the trials was higher than that in large contemporaneous registries, probably due to patient eligibility criteria for the trials, and the participation of higher quality centers for coronary revascularization. Nevertheless, procedural survival for PCI is significantly greater than for CABG in clinical registries. In randomized trials the freedom from procedural stroke was significantly higher with PCI (Figure 8).

Long-term survival was not substantially different between PCI and CABG up to five years after the initial procedure in the randomized trials. Summary survival differences indicated higher survival in CABG-assigned patients over PCI-assigned patients between six months and five years of less than one percent in absolute terms at each time point (Figure 11, Appendix C Figures 3-6). This conclusion differs somewhat from that of the meta-analysis reported by Hoffman and associates, who found a statistically significant survival advantage for CABG of 1.9 percent at five years based on the results of seven trials. Our analysis is based on a larger number of trials (12 with five years follow-up), and a greater representation of trials in which PCI was performed using stents. Five-year survival in our analysis of the "balloon-era" trials was significantly higher after CABG, whereas survival in the "stent-era" trials was not different between the procedures (Appendix C, Figure 17). Another difference is that our analysis included the AWESOME trial, which was excluded by Hoffman and associates, but our findings were unchanged in a sensitivity analysis that excluded the AWESOME trial. Thus, the most likely explanation for this difference between our results and those of Hoffman and associates is simply that our analysis was based on a more extensive data set with a greater number of more recent trials that used coronary stents routinely. Our analyses show that overall survival over one to five years was generally quite similar in PCI- and CABG-treated patients who were eligible for randomization to either procedure.

Overall freedom from angina and from repeat revascularization procedures strongly favored CABG over PCI (Figures 16 and 17). This difference may be the result of more complete anatomic revascularization with CABG than with PCI, or to restenosis after PCI or both. The advantage of CABG in freedom from angina diminished between one and five years of follow-up, but the difference of 5 percent at five years was nevertheless significant ($p<0.0001$). The difference between CABG and PCI in the need for repeat revascularization diminished from balloon-era trials to stent-era trials (Figure 18), but remained quite significant even in the most recent trials in which bare metal stents were used routinely for PCI.

Outcomes in Subgroups

The average outcomes reported by clinical trials and large registries may vary according to patient and provider characteristics. Our review suggests that while the overall outcome differences between PCI and CABG may widen or narrow somewhat in various patient subgroups, there was little evidence for neutralization or frank reversal of comparative effectiveness according to these factors. This conclusion is based more on an absence of evidence rather than on strong evidence that efficacy is unchanged according to patient characteristics, since statistical power was low in subgroup analyses and outcomes in subgroups have been reported sparsely, if reported at all.

The subgroup evidence is strongest for patients with diabetes and patients with more extensive coronary disease. There has been much debate about the finding of the BARI trial that CABG reduced mortality much more than PCI among patients with diabetes than in patients without diabetes. Our overview of all randomized trials (Figures 20 and 21) shows that the overall survival advantage of CABG over PCI in patients with diabetes was not statistically significant, averaging 0.8 percent in absolute terms at five years. The totality of the evidence from clinical trials suggests that the initial BARI finding may have been accentuated by the play of chance within the subgroup of patients with diabetes.

It has been shown previously that the survival advantage for coronary revascularization compared with medical therapy varies directly with the number of diseased vessels, which suggests that the comparative efficacy of PCI and CABG may also vary according to the number of diseased vessels. Trials enrolling patients with single-vessel proximal LAD disease had qualitatively similar results as trials enrolling patients with multi-vessel disease (Figure 12). Only a few trials specifically reported outcomes by number of diseased vessels—these suggest that CABG reduces mortality compared with PCI to a greater extent in patients with three-vessel disease than in patients with two-vessel disease. While this finding is not definitive, it is consistent with analyses from large clinical registries that show significant variation in comparative survival after PCI and CABG depending on the extent of coronary artery disease.

While most of the other patient characteristics such as age, gender, or presence of non-coronary vascular disease reduce long-term survival, they appear to decrease survival to a similar extent in patients treated with PCI or CABG. There is no strong basis, therefore, to alter the general conclusions about the relative effectiveness of PCI and CABG in these subgroups. Again, this conclusion must be tempered by the low statistical power of all subgroup analyses and the very spotty reporting by trials on these subgroups.

There was considerable evidence that the level of provider experience with CABG and PCI affects clinical outcomes. Procedural survival of both CABG and PCI decreased significantly in low volume hospitals and with low volume operators. While none of these studies was randomized, these findings are consistent with a large body of literature demonstrating a relationship between the volume of patients treated and patient outcomes for a wide variety of procedures.[219] The effect on procedural outcomes of PCI and CABG may be only modest, however, at least among sufficiently experienced centers and operators. Nevertheless, the persistence of this phenomenon even as the risk of PCI has been reduced by the availability of coronary stents and adjunctive therapy suggests that patients should be aware of the experience and outcomes of the specific center in which they will undergo coronary revascularization.

Generalizability of Randomized Trials of PCI Versus CABG

While randomized trials are accepted as the most definitive method to compare therapies, it is important to acknowledge the limitations in generalizing trial results to less selected patients and providers. The patients enrolled in the randomized trials of PCI versus CABG were selected to represent the "middle ground" in the spectrum of coronary artery disease, in that neither patients with very extensive coronary atherosclerosis (who generally receive CABG) nor patients with very limited coronary atherosclerosis (who generally undergo PCI) were enrolled (Tables 5 and 6). In addition, few patients enrolled in the trials were elderly, or had a left ventricular ejection fraction below 40 percent, or had heart failure. The findings from the randomized trials, and our synthesis of these results, do not necessarily apply to populations of patients who were not well represented in clinical trials.

Some insight into the comparative use and outcomes of PCI and CABG is provided by several large clinical registries, including the regional databases from Alberta, Canada,[147] New York State,[188] Northern New England,[201] and Scotland,[206] and the databases of the large referral centers at Duke[156, 159] and the Cleveland Clinic.[153] These registries document striking differences in the extent of coronary artery disease between patients selected for PCI and those selected for CABG. In the Duke series, for instance, 60 percent of PCI patients had single-vessel disease and nine percent had triple-vessel disease, whereas 58 percent of CABG patients had triple-vessel disease and nine percent had single-vessel disease.[159] The Cleveland Clinic Registry used a multivariable propensity score to quantify the probability a patient would undergo PCI rather than CABG, and reported the most significant predictors ($p<0.0001$) to be ejection fraction (PCI/CABG odds ratio 1.22 favoring PCI for every 10 percent increase), presence of a total coronary occlusion (PCI/CABG odds ratio 0.26), left main disease (PCI/CABG odds ratio 0.06), proximal left anterior descending disease (PCI/CABG odds ratio 0.45) and peripheral vascular disease (PCI/CABG odds ratio 0.38 favoring CABG). In the Cleveland data, the median propensity score of 0.52 (interquartile range 0.20 to 0.79) among the PCI patients was considerably higher than the median score of 0.03 (interquartile range 0.01 to 0.11) for CABG patients. These data from large registries show that in common clinical practice the typical patient undergoing PCI is quite distinct from the typical patient undergoing CABG, and suggest that few patients would be eligible for randomization because few would be considered to be a reasonable candidate for either PCI or CABG.

These large clinical databases have also compared survival of patients who have undergone PCI with that of patients who had CABG.[147, 153, 156, 159, 188, 201, 206] Since patients were not randomized, the registries used a variety of statistical methods to adjust for the observed and recorded differences between the two patient groups. In the overall patient populations in these registries, the CABG/PCI hazard ratio ranged from 0.43[153] to 0.86,[201] which differs substantially from the PCI/CABG odds ratio we found in our overview of randomized trials in patients with multi-vessel disease (PCI/CABG odds ratio for survival of 0.95 at five years of follow-up).

We believe that the difference in comparative efficacy of PCI and CABG reported by randomized trials and that reported by the registries is largely due to the differences in the patient populations, especially in their extent of coronary disease. Patients in the randomized trials all met specific entry criteria and could reasonably receive either PCI or CABG, whereas patients in the registries were relatively unselected and were typically eligible either for PCI or CABG, but not for both. The registry studies that compared PCI and CABG in different subgroups of coronary anatomy found very similar survival in the patients in the "middle ground" of the spectrum of coronary disease and, by contrast, much better survival with CABG than with PCI among patients with extensive coronary disease. In the Northern New England Registry, for instance, the adjusted CABG/PCI hazard ratio was 0.98 for double-vessel disease ($p=0.77$) and 0.60 for triple-vessel disease ($p<0.01$). In the Duke Databank,[156, 159] there was a significant inverse relationship between the extent of coronary disease and the CABG/PCI hazard ratio, with most of the survival advantage from CABG derived from patients with most severe coronary disease. Similar results were reported from the Alberta and Cleveland Registries and, to a lesser extent, from the New York State Registry.[188] We interpret these data as showing relatively little difference between PCI and CABG in survival among patients who would meet entry criteria for randomized trials, but a larger difference in patients with more extensive disease who were selected for CABG in the registries from the mid-1990s to 2001.

Evolving Revascularization Methods

The evidence we have summarized derives primarily from randomized trials conducted in the "balloon era" of 1987 to 1993, and the "bare-metal stent-era" of 1997 to 2001. There are very few trial data that compare the most recent drug-eluting stent technology with contemporary CABG. While several randomized trials are ongoing, results will not be available for several years, especially for long-term outcomes. While some have argued that older PCI vs. CABG trials are now "obsolete," the evidence does not support the contention that survival and freedom from myocardial infarction have changed as a result of the most recent revascularization methods. Specifically, quantitative overviews have reported no difference in survival and freedom from myocardial infarction between patients randomized to either bare-metal stents or to balloon angioplasty,[8] or between patients randomized to either drug-eluting stents or bare-metal stents.[9] Nor is there any higher incidence of survival or freedom from MI between patients randomized to minimally invasive or off-pump CABG compared with standard CABG techniques.[229, 230] The technical improvements in coronary revascularization clearly do reduce the need for repeat procedures (PCI) and shorten perioperative recovery time (CABG), but these improvements should not be extrapolated to imply that hard events (death and myocardial infarction) have been reduced as well.

Background medical therapy for coronary disease has dramatically improved since the mid-1980s with the introduction of new drugs and the completion of large clinical trials that demonstrate reduced cardiac events. Medical therapy is recommended for all patients after PCI and CABG, so the comparative efficacy of these two procedures should not change drastically as a result of better medical therapy. Nevertheless, to the extent that the overall risk of patients with coronary disease has been reduced by improved medical therapy, any risk differences between PCI and CABG are also likely to be reduced. More importantly, the efficacy of coronary revascularization in increasing survival and freedom from myocardial infarction compared with medical therapy may also have been reduced over the past 20 years. While a comparison of PCI or CABG with medical therapy is beyond the scope of this report, we note that several clinical trials (e.g., BARI-2D, COURAGE) are ongoing and will compare contemporary aggressive medical therapy with revascularization plus medical therapy.

Future Research

This comprehensive review of the comparative effectiveness of PCI and CABG has identified numerous gaps in evidence that would be suitable for future research. The paucity of published analyses of PCI and CABG outcomes according to patient characteristics strongly suggests the value of a collaborative pooling of individual patient-level data from the randomized trials to a) enhance statistical power to identify subgroup effects, and b) reduce publication bias by including data from all trials. The stent trialists collaboration has pooled one-year outcomes of four trials (ARTS, ERACI-II, MASS-II, and SOS), and provided useful short-term analysis in key subgroups.[17] The planned extension of this collaborative pooling to include five year follow-up data will be very informative.

A more extensive collaborative study to pool individual patient data from both balloon-era and stent-era trials would provide additional advantages. First, the number of patients and outcome events would be greatly increased, thereby improving statistical power even further in patient subgroups. Second, more direct assessments of the impact of stents upon the comparative effectiveness of PCI and CABG would be feasible, as well as assessment of whether relative efficacy changes over extended follow-up.

Further clinical trials are also needed to assess whether the availability of drug-coated stents have affected the comparative efficacy of PCI and CABG. Such trials are particularly warranted, as pooled studies suggest that survival and freedom from myocardial infarction are not different between bare metal stents and drug-coated stents over medium-term follow-up. Recent safety concerns about drug-coated stents emphasize the need for extended follow-up and trials large enough to detect clinically meaningful differences in outcomes. Several trials are currently underway to compare CABG with PCI using drug-coated stents (Appendix C Table 13).

While there is extensive literature examining the effect of hospital volume and physician volume on the outcomes of PCI and CABG, our review indicates several major gaps that should be addressed in further research. The new, minimally invasive approaches to CABG have not been examined in much detail with respect to procedure volume and outcome, and it cannot be assumed that the relationships defined for standard CABG will apply to minimally invasive CABG. In particular, the volume thresholds for minimally invasive CABG are likely to be different, given the difference in technique. A broader issue in all volume-outcome research is

that procedural mortality is not the only important measure of outcome. Procedural myocardial infarction, graft patency, relief of angina, and long-term outcomes are also pertinent to decision making and should be explored in relation to volume levels. Finally, process measures have been increasingly used to measure quality of care when there is a strong evidence base linking process to outcome. Research to establish evidence-based process measures for coronary revascularization might provide better metrics for quality of care for PCI and CABG procedures. However, these measures may be more cumbersome to collect, such that volume measures may still be valuable if the relationship between process, volume, and outcome were better defined.

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Abbreviations

Acronym/Abbreviation	Definition
AHRQ	Agency for Healthcare Research and Quality
BMI	Body Mass Index
BMS	Bare Metal Stent
CABG	Coronary Artery Bypass Grafting
CAD	Coronary Artery Disease
CCS	Canadian Cardiovascular Society
CER	Comparative Effectiveness Review
DES	Drug-Eluting Stent
EF	Ejection Fraction
EPC	Evidence-based Practice Center
HTN	Hypertension
LAD	Left Anterior Descending Artery
LCX	Left Circumflex Artery
LIMA	Left Internal Mammary Artery
LV	Left Ventricle
LVEF	Left Ventricular Ejection Fraction
MeSH	Medical Subject Headings
MI	Myocardial Infarction
MIDCAB	Minimally Invasive Direct Coronary Artery Bypass
MVD	Multi-vessl Disease
NYHA	New York Heart Association
PCI	Percutaneous Coronary Intervention
PVD	Peripheral Vascular Disease
RCA	Right Circumflex Artery
RCT	Randomized Controlled Trial
SCHIP	State Children's Health Insurance Program
SRC	Scientific Resource Center
SVD	Single-Vessel Disease
TIA	Transient Ischemic Attack
TMI	Transmyocardial Revascularization
UK	United Kingdom
US	United States of America