THERAPEUTICS INITIATIVE Evidence Based Drug Therapy

Review & Update 1998

Our last update was at the end of 1996. In this issue we summarize the findings of 6 randomized controlled trials (RCTs) and synthesize the evidence from these trials in the context of previous letters relating to treatment of hypertension (# 7,8,9,16), Type 2 diabetes (#23), Lipid lowering therapy (# 25), and olanzapine (Letter #20).

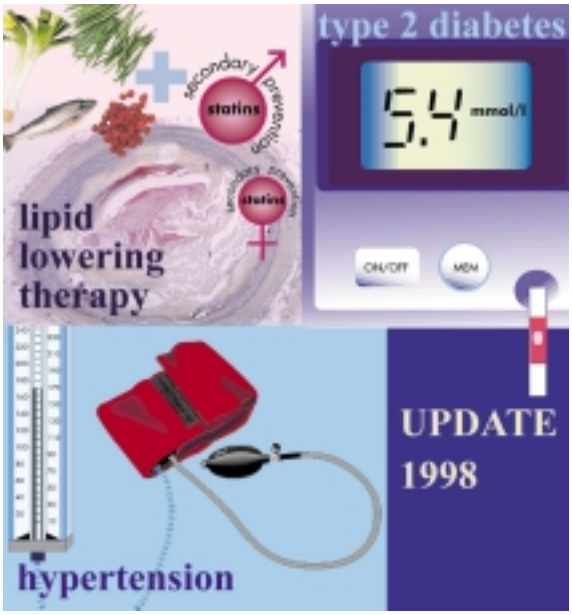
Treatment of Hypertension

The SYST-EUR trial[1] compared active treatment with placebo in older patients with isolated systolic hypertension. A dihydropyridine calcium channel blocker (CCB), nitrendipine, was first-line treatment (enalapril, hydrochlorothiazide or both were second and third line drugs). **These results can be compared to the SHEP trial, where chlorthalidone was first-line therapy.**

	Total CV events		ARR %	NNT	Dur. yrs
	control%	treatment %			
SYST-EUR	8.1	5.7	2.4	42	2.1
SHEP	18.4	12.0	6.4	16	4.5

ARR = absolute risk reduction
NNT = number needed to treat to prevent one event

The Hypertension Optimal Treatment **(HOT) trial[2]** had 2 objectives: 18,790 patients with hypertension were randomly assigned to one of 3 target diastolic pressures, ≤90 mm Hg, ≤85 mm Hg, or ≤80 mm Hg, and to 75 mg/day acetylsalicylic acid or placebo. There was no placebo group so overall effectiveness could not be determined. Step therapy was predefined: **1:** felodipine 5 mg/day, **2:** ACE inhibitor or beta blocker, **3:** 10 mg felodipine, **4:** double dose step 2 drug, and **5:** thiazide. A 2 mm Hg difference in systolic and diastolic blood pressure was attained between each of the 3 target groups. **The 2 groups with lower BP might be expected to have fewer cardiovascular events, but this was not seen**; the primary outcome measure, major cardiovascular events, was similar for the 3 groups, 3.7%, ≤90 mm Hg, 3.7%, ≤85 mm Hg, and 3.5%, ≤80 mm Hg. Subgroup analysis of the 8% of patients with Type 2 diabetes at baseline did show total cardiovascular events lower in the ≤80 mm Hg group, 4.4%, than the ≤90 mm Hg group, 9.0%, ARR = 4.6%, NNT = 22 for 3 yrs. In the non-diabetic patients (92% of population) there was a trend towards an increased mortality with a greater



intensity of treatment (2.7% ≤90 mm Hg, 2.9% ≤85 mm Hg, 3.3% ≤80 mm Hg, p= 0.07). The incidence of side effects at 24 months was not statistically different between the 3 target groups. **Aiming for a target diastolic BP of lower than 90 mm Hg provides no therapeutic advantage for most hypertensive patients.**

A small statistically significant decrease in total cardiovascular events was seen with ASA (3.3%) as compared to placebo (3.9%), ARR = 0.6%, NNT = 175 for 3.8 yrs. This difference became non-significant when silent myocardial infarctions were included as an event. ASA therapy was associated with an increased risk of non-fatal major and minor bleeds (3.0% *v* 1.6%) absolute risk increase (ARI) = 1.4%, number needed to treat to harm one patient (NNH) = 74 for 3.8 yrs. **Benefits of ASA do not exceed risks in an unselected group of hypertensive patients.**

Treatment of Type 2 Diabetes

The UK Prospective Diabetes Study (UKPDS)[3-6] randomised newly diagnosed Type 2 diabetics (N = 3867) to conventional therapy or intensive therapy with sulfonylureas (chlorpropamide, glyburide) or insulin[3]. Conventional therapy included drug treatment only if fasting blood glucose was >15mmol/L or symptoms of hyperglycemia developed. Intensive treatment with sulfonylureas or insulin reduced HbA1C to 7.0 % as compared to 7.9% over the 10 years of the study. The primary outcome, any of 21 diabetes related endpoints, was significantly reduced by intensive treatment, 35.3% *v* 38.5%, ARR = 3.2%, NNT = 31 for 10 yrs.

This difference was predominantly due to reduction in the microvascular complication, retinopathy requiring photocoagulation. Cardiovascular events were not significantly reduced; there was a trend towards reduction in total MI, 14.2% *v* 16.3%, p=0.052. There were no significant differences in outcome between the different sulfonylureas or insulin. Over the first 10 years intensive therapy increased major hypoglycemic episodes: conventional therapy, 1%, chlorpropamide, 4%, glyburide, 6%, and insulin, 23%. Intensive therapy also caused greater weight gain than conventional therapy: insulin, 4.0 kg, chlorpropamide, 2.6 kg and glyburide, 1.7 kg.

In the same trial 1704 overweight diabetic patients were randomised to metformin, conventional therapy or intensive treatment with sulfonylureas or insulin. Incidence of any diabetes endpoint was significantly reduced by metformin, 28.7% (ARR = 10.2%, NNT = 9 for 10.7 yrs) as compared to conventional, 38.9%, or intensive, 36.8%, therapy. Diabetes related deaths, total mortality and total myocardial infarctions were also significantly reduced by metformin[4]. Metformin caused no increase in major hypoglycemic episodes and no weight gain as compared to conventional therapy. In a separate RCT when patients on maximal sulfonylurea therapy were randomised to added metformin or placebo no benefit was seen from adding metformin over a 6.6 year period. **For first-line Type 2 diabetes therapy the benefit/risk ratio for metformin is many fold greater than that for sulfonylureas or insulin.**

In the same trial 1148 patients with hypertension were randomly allocated to tight blood pressure control or to less tight control[5]. The tight control group was randomized to captopril or atenolol; the second-line drug was furosemide. ACE inhibitors and beta blockers were not used in the less tight control group. The mean blood pressure for tight control was 144/82 mm Hg as compared to 154/87 mm Hg. Tight control resulted in a significant reduction in any diabetes endpoint, 34.1% v 43.5%, ARR = 9.4%, NNT = 11 for 8.4 yrs. Diabetes related death, stroke, and microvascular disease were also significantly reduced. **There were no significant differences between captopril and atenolol** in blood pressure reduction or any outcome parameter, including progression of albuminuria[6].

The benefits achieved from intensive blood pressure reduction in Type 2 diabetes are of similar magnitude to those achieved with metformin.

Lipid lowering therapy

The AFCAPS[7] and LIPID[8] trial add to our outcome data with statins. All trials were for approximately 5 years; women were under-represented, <15% overall. **The chances that a patient will benefit from treatment with a statin becomes very small as the risk (event incidence in control group) decreases.**

Trial type	Statin	$\bar{x}$ Chol ❖ mmol/L	Events* control %	Events* ARR %	NNT
4S (2^o)	Simva -	6.7	21.5	8.0	13
LIPID (2^o)	Prava -	5.6	17.2	3.9	26
CARE (2^o)	Prava -	5.4	13.7	2.7	37
WOS (1^o)	Prava -	7.0	8.4	2.6	38
AFCAPS (1^o)	Lova -	5.7	3.6	1.4	71

2^o = secondary prevention ❖ = Average baseline cholesterol
1^o = primary prevention * = Total MI or CV death

Olanzapine

The full 28-week trial comparing olanzapine (17.2 mg/day) with risperidone (7.2 mg/day) showed fewer extrapyramidal side effects with olanzapine (18.6% *v* 31.1%) and greater weight gain with olanzapine (4.1 kg *v* 2.3 kg)[9]. Details of the previously noted cases of leukopenia with olanzapine have now been published; in all 3 cases olanzapine was associated with an accentuation and prolongation of granulocytopenia in patients who had not fully recovered from clozapine-induced granulocytopenia[10]. The risk of granulocytopenia with olanzapine appears to be similar to other antipsychotics like haloperidol and risperidone.

This Letter contains an assessment and synthesis of published (and whenever possible peer-reviewed) publications up to Dec.1,1998. We attempt to maintain the accuracy of the information in the Therapeutics Letter by extensive literature searches and verification by both the authors and the editorial board. In addition this Therapeutics Letter was submitted for review to 54 experts and primary care physicians in order to correct any identified shortcomings or inaccuracies and to ensure that the information is concise and relevant to clinicians.

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