SMH ST. MICHAEL'S HOSPITAL Cardiology
UNIVERSITY OF TORONTO
A REPORT BY THE DIVISION OF CARDIOLOGY
ST. MICHAEL'S HOSPITAL, UNIVERSITY OF TORONTO
Scientific Update™

Results of clinical trials: Implications for cardiovascular care

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Satellite Symposium at the Ninth European Meeting On Hypertension

Milan, Italy June 12-14, 1999

Reported and discussed:
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Hypertension is a common disorder and an important risk factor for cerebrovascular and cardiovascular disease. Patients with hypertension often have other risk factors and co-morbid conditions such as diabetes mellitus, hypercholesterolemia, smoking, and coronary artery disease. The interaction between these factors and hypertension is well-documented. For example, diabetic hypertensives are twice as likely to experience morbid cardiovascular events as nondiabetic hypertensives.[1] In the United Kingdom Prospective Diabetic Study (UKPDS), aggressive blood pressure (BP) reduction resulted in a 32% reduction in the risk of diabetes-related mortality.[2] The following report highlights recent analyses of completed and ongoing clinical trials that may provide further insight into how secondary risk factors influence the response to antihypertensive therapy and what impact newer agents, such as calcium channel blockers (CCBs), may have on cardiovascular and other morbid events.

Can CCBs improve prognosis in older diabetic patients with isolated systolic hypertension?

Two studies (FACET and ABCD), comparing the effects of angiotensin-converting enzyme (ACE) inhibitors and CCBs in patients with hypertension and noninsulin dependent diabetes, have demonstrated that ACE inhibitors have a more favorable impact on cardiovascular outcome than the CCBs.[3,4] These results raised the suspicion that CCBs might exert harmful effects in these patients. In order to clarify this issue, a post-hoc analysis of the results of the Systolic Hypertension in Europe (Syst-Eur) Trial was recently conducted to investigate the outcome of treated diabetic and nondiabetic patients.[5]

Syst-Eur was a large multicenter trial designed to evaluate whether treatment of isolated systolic hypertension in the elderly reduced the incidence of the combined endpoint of fatal and nonfatal stroke.[6] Key inclusion criteria included age ≥60 years, sitting systolic blood pressure (SBP) of 160-219 mm Hg and diastolic blood pressure (DBP) ≤95 mm Hg. After stratification for centre, sex, and previous cardiovascular complications, 4,695 patients were randomized to the CCB nitrendipine (10-40 mg daily), and subsequent stepwise addition of enalapril (5-20 mg daily), and hydrochlorothiazide (12.5-25 mg daily), or placebo. The results of Syst-Eur were discussed in a previous issue of *Scientific Update*. The trial was stopped early because of the results favoring active therapy. At a median of 2 years' follow-up, the total rate of stroke was reduced by 42% (p=0.003); nonfatal strokes were reduced by 44% (p=0.007); and total cardiac events were reduced by 26% (p=0.03). Syst-Eur therefore demonstrated that stepwise hypertensive treatment – starting with the dihydropyridine CCB nitrendipine – reduces the incidence of stroke and cardiovascular complications in elderly patients with isolated systolic hypertension. Furthermore, in this

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The topics presented in *Cardiology Scientific Update* are independently determined and the content authored exclusively by physician-members of the Division of Cardiology, St. Michael's Hospital. This publication is made possible by unrestricted funding from the publisher, Snell Medical Communication Inc., which has received educational grants from the pharmaceutical industry in support of this work.

Table 1: Reduction of clinical events of the diabetic and non-diabetic patients in the Syst-Eur study

	Diabetic n=492	Non-diabetic n=4203	p-value diabetic vs non-diabetic
All strokes	73%	38%	NS
All cardiovascular endpoints	69%	26%	0.01
All-cause mortality	55%	16%	0.04
Cardiovascular mortality	76%	24%	0.02

patient population, the use of CCBs appears to be safe and not accompanied by detrimental outcomes.

In the Syst-Eur study, at randomization, 492 patients (10.5%) had diabetes. At two years, the net difference in BP between the placebo- and active-treatment groups was 8.6 mm Hg for SBP and 3.8 mm Hg for DBP in diabetic patients. In the 4,203 nondiabetics, the difference was 10.3 mm Hg and 4.6 mm Hg, respectively. The percent reduction of endpoints for the diabetics and nondiabetics is shown in Table 1. In diabetic patients, active treatment resulted in a marked reduction in all-cause mortality, cardiovascular mortality, fatal and non-fatal strokes, and all cardiac endpoints. The reduction of these events in nondiabetics was more modest and the differences in reduction between diabetic and nondiabetic patients were significant for total mortality, cardiovascular mortality, and all cardiovascular endpoints. The limitations of 'post-hoc' analysis notwithstanding, these data strongly suggest that CCB-based antihypertensive therapy is beneficial in older diabetic patients with isolated systolic hypertension.

A recent subgroup analysis of the Systolic Hypertension in China (Syst-China) trial also appears to support the above conclusion. The design of Syst-China was similar to the Syst-Eur trial.[6,7] In the placebo-treated group in Syst-China, the presence of diabetes significantly raised the risk of five endpoints by two- to threefold.[8] However, active treatment, starting with nitrendipine, reduced the excessive risk associated with diabetes to a nonsignificant level. Findings from subgroup analysis of the Syst-Eur and Syst-China trials do not lend support to the hypothesis that long-acting CCBs may be harmful in diabetic patients. It is likely that the results of FACET and ABCD can be explained by the superior cardiovascular protective effect of the ACE inhibitors, rather than by a detrimental effect of CCBs on hypertensive patients with diabetes. These hypotheses are further supported by the large and recently reported HOT trial where antihypertensive therapy based on felodipine resulted in significant benefit in relation to lowering BP, especially in diabetic patients.[9,10]

The INSIGHT Study: Reducing cardiovascular risk by lowering BP in high-risk essential hypertension

Hypertension is a key risk factor associated with the development of atherosclerosis and cerebrovascular and cardiac events. Despite a great deal of knowledge about the interaction of several risk factors with hypertension in determining cardiovascular disease, so far most outcome trials have focused on only one risk factor such as noninsulin dependent diabetes reported earlier.

The INSIGHT study is a multi-center trial that compares fatal and nonfatal cardiovascular endpoints in high-risk hypertensive patients randomized to either nifedipine GITS or a hydrochlorothiazide/amiloride combination. Importantly, in this study, patients must have at least one additional risk factor besides hypertension. The goal is to detect a 25% lower rate of cardiovascular and cerebrovascular morbid events in nifedipine GITS as compared to those patients receiving the diuretic combination. Recruitment for INSIGHT began in September, 1994, and was completed on May 1, 1996. Nine countries participated in the study and follow up is still ongoing.

In total, 7,302 patients have entered the run-in phase of the trial. but 848 patients had to be withdrawn for various reasons before randomization. Therefore, 6,454 patients (88% of those recruited) were randomized. There were 2,996 men and 3,458 women. The mean age was 65 years in men and 66 in women. For the whole group, SBP and DBP were 172 and 99 mm Hg, respectively, with no difference between men and women. Only 13% of patients had hypertension diagnosed for the first time when they entered the study. Fifty five percent of patients had only 1 risk factor

in addition to hypertension, 34% had 2, 9% had 3, and 2% had 4 additional risk factors. Hypercholesterolemia was the most prevalent secondary risk factor (55%), followed by smoking history (29%), diabetes (20%), and family history of coronary artery disease (20%). Proteinuria was the least frequent secondary factor (3%). In terms of combined risk factors, the combination of smoking and hypercholesterolemia was the most prevalent (11%). Hypercholesterolemia plus a positive family history (8%), and hypercholesterolemia plus diabetes were also prevalent. The distribution of risk factors was comparable in men and women and also from one country to another.

Although the study is still ongoing, examining the INSIGHT data gives insight regarding the efficacy of treatment. Diabetic patients appear to be the most resistant to therapy, requiring a second and third drug more frequently to achieve target BPs. Interestingly, the best predictor of response was pulse pressure with opposite effects on SBP and DBP, indicating that patients with isolated systolic hypertension are slightly more responsive to treatment.

CCBs and prevention of dementia: Results of the SYST-EUR trial

Systolic hypertension increases the risk of dementia in the elderly. The Syst-Eur Vascular Dementia project was a substudy of Syst-Eur designed to investigate whether antihypertensive treatment reduces the incidence of dementia in elderly patients with systolic hypertension.

Eligible patients were non-demented, at least 60 years old, and had a sitting BP ranging from 160 to 219 mm Hg SBP and <95 mm Hg DBP. The treatment assignment of Syst-Eur is described above. Cognitive function was assessed by the Mini-Mental State Examination (MMSE). If the MMSE score was ≤23, the diagnosis was established based on the DSM-III-R criteria. The cause of dementia was established using either the Modified Ischemic Score with brain imaging or the Hachinski score.

The median MMSE score at randomization was 29 in both treatment groups and the median BP was 173/86 mm Hg. The incidence of dementia was reduced by 50%, from 7.7 cases per 1000 patient-years in the placebo group (n=1180) to 3.8 cases in the active treatment group (n=1238) (21 versus 11 patients, p=0.05). Alzheimer type dementia was reduced as well as vascular or mixed dementia. At the last evaluation, SBP and DBP were reduced by 8.3 and 3.8 mm Hg, respectively (p<0.001) in the active treatment group. On average, MMSE scores did not change in either group.

Antihypertensive therapy initiated with the dihydropyridine CCB, nitrendipine, reduced the incidence of dementia by 50%. Treating 1000 hypertensive patients for 5 years, therefore, could prevent 19 cases of dementia.

Endothelial dysfunction – A surrogate endpoint in cardiovascular disease? Update on the ENCORE trial

The endothelium plays a crucial role in cardiovascular regulation.[11,12] Central to endothelial function is the mediator nitric oxide (NO), formed by the endothelial isoform of nitric oxide synthase (eNOS).[12,13] NO is released by mechanical forces and acetylcholine, bradykinin, ADP/ATP, and serotonin. NO is not only a potent vasodilator, it also inhibits platelet aggregation, smooth muscle cell proliferation, monocyte adhesion, as well as the expression of adhesion molecules.[12] In many clinical conditions, including most of the cardiovascular risk factors such as aging, hypertension, hypercholesterolemia, smoking, and diabetes mellitus, NO availability is reduced primarily by the production of oxygen-free radicals that break it down. A dysfunctional endothelium not only loses its ability to protect the vessel wall, it can also induce vascular damage, in particular atherosclerosis. Hence, an important aim of cardiovascular treatment is to reverse endothelial dysfunction.

Several classes of agents including the ACE inhibitors, CCBs and the statins have been shown to improve endothelial function by increasing NO availability.[14] CCBs have been implicated to exert an anti-atherogenic effect and a beneficial influence on endothelial function.[15,16] This beneficial effect appears to be mediated, at least in part, by an increase in NO availability[14] brought on by the antioxidant effect of agents such as nifedipine.[17] This hypothesis is confirmed by preliminary results demonstrating that treatment with nifedipine GITS can restore NO availability in patients with hypercholesterolemia.[14]

Another class of drugs that can improve endothelial function is the statins. There is evidence to suggest that treatment with statins can increase the availability of NO and therefore improve endothelial function.[18,19] Furthermore, there is also speculation that the beneficial effect of the statins may not be entirely dependent on the reduction

of plasma cholesterol levels, suggesting that additional mechanisms may be operative.[20]

The above-mentioned observations form the rationale for the Evaluation of Nifedipine and Cerivastatin On Recovery of Endothelial Function (ENCORE) trial. The study is divided into two parts.

• In ENCORE I, the objective is to evaluate the effect of nifedipine and cerivastatin on endothelial function in patients with coronary artery disease. Four hundred patients undergoing percutaneous transluminal coronary angioplasty (PTCA) for single-vessel disease will be studied. These patients will be randomized to placebo, nifedipine GITS 30-60 mg daily, cerivastatin 400 µg daily, or a combination of nifedipine and cerivastatin. Endothelium-dependent responses to acetylcholine using quantitative coronary angiography, as well as microvascular response to adenosine, will be studied at baseline and at 6 months. At the time of writing, 230 patients have been studied.

• In ENCORE II, the objective is to assess whether changes in endothelial function are related to structural coronary vascular changes. Patients will be randomized to cerivastatin 200 µg daily, combined therapy with nifedipine GITS 60 mg daily and cerivastatin 800 µg daily, or cerivastatin 800 µg daily. Response to acetylcholine as well as intravascular ultrasound will be studied at baseline and after two years of therapy.

ENCORE will determine whether the long-acting nifedipine and/or the statins improve endothelial function and the atherosclerotic process in patients with coronary artery disease.

Conclusion

In summary, results of clinical trials presented in this review underscore the importance of adequate control of BP in hypertensive patients. The beneficial effects of BP-lowering are more pronounced in patients with co-morbid conditions such as diabetes. Furthermore, subgroup analyses of Syst-Eur and Syst-China both attest to the efficacy and safety of long-acting CCBs in diabetic hypertensives. Large-scale clinical trials are underway to evaluate the impact of antihypertensive therapy in patients with multiple risk factors as well as its effect on the surrogate endpoints of cardiovascular disease.

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