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™

The Changing Paradigm of Hypertension Management: Optimal Care of Patients with Multiple Risk Factors

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18th Scientific Meeting of the International Society of Hypertension

Chicago, Illinois August 20, 2000

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Hypertension is among the most common and serious modifiable risk factors for cardiovascular and renal disease. However, the condition remains relatively poorly detected and under-treated. Until recently, outcome trials in hypertension involved the use of diuretics and ß-blockers in the overall hypertensive population. Within the past three years, we have witnessed a number of clinical trials that have focused attention on "newer" antihypertensive agents, more intensive blood pressure lowering goals, and the targeting of high-risk patient populations. Results of these trials may lead to new paradigms of hypertension management.

New insights from clinical trials in hypertension

Treatment of severe hypertension has markedly decreased renal failure, heart failure, and malignant hypertension. Unfortunately, the condition is still relatively poorly detected and certainly under-treated.[1] The initial outcome trials of hypertension involved regimens based on diuretics or ß-blockade therapy.[2] The results of these trials suggested that treatment of mild-to-moderate hypertension decreases the incidence of stroke by 30-40% and heart failure by 40%. More recent controlled trials in hypertension tested the impact of newer drug classes on clinical outcomes,[3-10] using mostly diuretics and/or ß-blockers as active controls. The results of these trials, as summarized in Table 1, suggest that regimens based on "newer agents" such as angiotensin-converting enzyme inhibitors (ACEIs), dihydropyridine calcium channel blockers (CCBs), or diltiazem, reduce cardiovascular (CV) events in the *general* hypertensive population to an extent comparable to that observed with the "older agents." The selective α-adrenergic receptor blocker doxazosin appeared to produce adverse CV outcomes compared to diuretic treatment.[10] One study also demonstrated the benefits of reducing isolated systolic hypertension in elderly patients with a dihydropyridine CCB.[7,8]

The Heart Outcomes Prevention Evaluation (HOPE) study, despite demonstrating a remarkably beneficial effect on outcomes with the ACEI ramipril,[11] addressed mainly a high risk patient population that was probably quite different from patients in the other hypertension outcome trials. Overall, at least for the *general* hypertensive population, the reduction in CV events by treatment is likely closely linked to a blood pressure-lowering effect across the classes of agents examined.

A second issue that has been addressed recently is the impact of controlling blood pressure (BP) target levels. The Hypertension Optimal Treatment (HOT) study demonstrated no significant differences in outcomes with lower BP in the general cohort of hypertensive patients.[12] However, there was a substantial benefit from more rigorous BP control in patients who had hypertension and diabetes. Other trials such as the UKPDS and the Syst-Eur studies have also demonstrated benefit from tight BP control in diabetic patients, regardless of the type of antihypertensive agents used.[3,8,13]

When the obverse of the outcome in the hypertension outcomes trials is considered, it is apparent that current management of hypertension fails to prevent 84% of myocardial infarctions (MI), 60% of all strokes, and 75% of all CV complications. MIs far outnumber strokes in patients with mild-

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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. *Cardiology Scientific Update* is made possible by unrestricted funding from the publisher, Snell Medical Communication Inc., which has received educational grants from the pharmaceutical industry for the distribution of this publication.

Table 1: Outcome trials in hypertension using newer classes of agents					
Drug	Study[3-10]	Controls	Mortality (Risk Ratio)		
			CV	CHD	Stroke
Captopril	UKPDS	BB	1.10	1.20	1.12
Captopril	CAPPP	T/BB	1.05	0.96	1.25*
Felodipine/isradipine	STOP-2	T/BB	0.99	1.10	0.88
Diltiazem	NORDIL	T/BB	1.01	0.99	0.97
Doxazosin	ALLHAT	T	1.25	1.03	1.19*
Enalapril/lisinopril	STOP-2	T/BB	0.94	0.90	0.90
Nifedipine	INSIGHT	T	1.01	1.12	0.97

CV, cardiovascular; CHD, coronary heart disease; T, thiazide diuretics; BB, β-blockers; * statistically significant

to-moderate hypertension and the failure to prevent MI is therefore central to the relatively disappointing general outcome of antihypertensive treatment. Recent trials have shown that aspirin and the statins each reduce MI by about 30% in hypertensive patients.[12,14,15] Accordingly, combined treatment with antihypertensive agents, aspirin, and statins may therefore reduce stroke by 40% in primary prevention and 70% in secondary prevention. The safe use of aspirin and judicious use of statins for primary prevention require formal estimation of coronary heart disease (CHD) risk using multiple risk factors.[14,16,17] Formal CHD risk assessment is also useful for treatment decisions in uncomplicated mild hypertension.[16,17] The effectiveness of treating two subjects with comparable degrees of hypertension, but different risk factor profiles, is depicted in Table 2. Much better returns from hypertension treatment can be attained by identifying all hypertensive subjects in the population, estimating their CHD risk, prescribing antihypertensive drug regimens that will effectively reduce systolic as well as diastolic BP to the appropriate target level,

Table 2: Cardiovascular risk and the risk/benefit of treating two hypertensive patients		
Blood pressure	150/92	150/92
Gender	Female	Male
Age (years)	24	70
Total cholesterol (mmol/L)	5.0	8.4
Diabetes mellitus	-	+
Left ventricular hypertrophy	-	+
CV event rate (10 years)	0.5%	76.5%
NNT (10 years)	1000	7

CV = cardiovascular
NNT = number of patients needed to treat

and using aspirin and statins in addition when appropriate. Obviously, to achieve these returns, better methods of screening, follow-up and attaining treatment targets are needed.

Diabetes and target-organ protection: Results from recent clinical trials

Cardiovascular protection

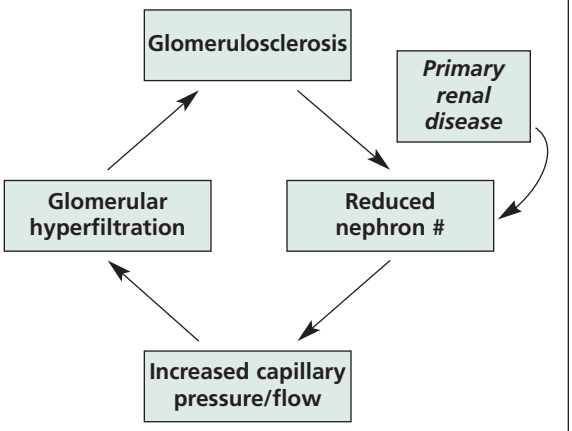
Recent outcome trials have suggested new paradigms for managing hypertensive patients with diabetes mellitus.

• The United Kingdom Prospective Diabetes Study (UKPDS) was a large, randomized trial of 9 years duration, designed to determine whether tight BP control prevents vascular complications in patients with type 2 diabetes.[13] The results clearly demonstrated a decrease in macrovascular and microvascular complications in patients treated to a lower goal of BP. The "tight control" group maintained a BP of 144/82 mm Hg, compared to "less tight control," defined as blood pressure <154/87 mm Hg. It is noteworthy that 29% of patients in the tight control group required more than 3 drugs. The benefits appeared to be accrued evenly between those treated with the ß-blocker atenolol or the ACEI captopril.

• The HOT study, briefly alluded to earlier,[12] assessed the effects of reducing diastolic BP to ≤90, 85, or 80 mm Hg on clinical outcomes. A dihydropyridine CCB, felodipine, served as the basis of therapy with the addition of other agents as needed to achieve target BP response. In the diabetic subpopulation, a target diastolic BP ≤80 mm Hg was associated with the lowest incidence of CV events. Again, combination therapy was required in 74% of patients in the lowest target BP group.

These trials therefore underscore the importance of attaining a specific goal of blood pressure lowering in hypertensive patients with diabetes or renal insufficiency as suggested in JNC VI and the Canadian Hypertension Guidelines.[18,19] The latest Canadian Guidelines for Hyperten-

Figure 1: Schematic representation of the mechanism of progression of renal disease



sion[19] recommend "newer" antihypertensive agents as preferred therapies (ie, long-acting dihydropyridine CCBs) to treat uncomplicated hypertension in patients over 60 years of age, and ACE inhibitors in patients under the age of 60.

• The Systolic Hypertension In Europe (Syst-Eur) trial was the first randomized, double-blind, placebo-controlled trial to examine the effects of newer classes of antihypertensive therapy in patients with isolated *systolic* hypertension.[7,8] The main findings have been reviewed in previous issues of *Cardiology Scientific Update*. Syst-Eur included 492 patients with diabetes among the 4695 patients studied. The long-acting dihydropyridine CCB, nitrendipine, was used as the initial agent followed by enalapril, and/or hydrochlorothiazide. After a mean duration of 2 years, the trial was stopped because of a 42% decrease in strokes and a 26% reduction in all cardiac events in the active-treatment group. Most importantly, the reductions in CVS events were seen in both diabetic and non-diabetic patients, and indeed active treatment eliminated excess CV risk among the diabetic subgroup.[8]

Renal protection

A schematic representation of the mechanism of progression of renal disease is depicted in Figure 1. The key abnormality is increased glomerular pressure/flow and glomerular hyperfiltration. The ACEIs decrease glomerular filtration pressure, thereby glomerular damage, particularly in the setting of diabetic nephropathy.[20] In animal models of diabetes, ACEIs appeared to reduce glomerular volume by retarding glomerular basement membrane thickening and the development of albuminuria. These effects may have a beneficial impact on trophic processes involved in progressive renal injury, and may attenuate vascular hypertrophy. This therapeutic construct has subsequently been validated in clinical trials in the use of ACEIs in patients with diabetes and hypertension.[21]

CCBs also have the ability to maintain or augment the glomerular filtration rate (GFR) in the face of vasoconstriction. These agents also have diverse properties, independent of their renal microcirculatory effect, that confer renal protection. These putative mechanisms include decreasing renal hypertrophy, attenuating mesangial entrapment of macromolecules, decreasing nephrocalcinosis and mitigating the mitogenic effects of diverse growth and inflammatory mediators.[20,22]

Two trials have recently extended these theoretical constructs to a clinical level. Velussi et al. reported the results of a 3-year study comparing the CCB amlodipine and the ACEI cilazapril in patients with hypertension and non-insulin dependent diabetes.[23] The decline in GFR per year was similar for both groups. A recent report from the Appropriate Blood Pressure Control in Diabetes (ABCD) study also demonstrated the equivalence of CCB and ACEI in renal protection.[24] In the ABCD study, 470 patients were randomized to treatment with either the CCB nisoldipine or enalapril. During the 5-year follow up, there was no difference between the 2 groups with respect to creatinine clearance. The results of these studies overall suggest that dihydropyridine CCBs and ACEIs are equally effective in renal protection.

Systolic pressure or pulse pressure: predictors of cardiovascular risk

Systolic hypertension in the elderly is often associated with a widening of the pulse pressure (increased systolic and decreased diastolic pressure). This is due in part to the loss of elasticity of large conduit vessels and is associated with increased amplitude of wave reflection which increases the pulse wave velocity in the stiff atherosclerotic vessel.[25] Recently, pulse pressure has captured considerable clinical interest as an independent marker of risk for CV events, including stroke and heart failure.[26,27]

Isolated systolic hypertension definitely increases the risk of carotid atherosclerosis,[28] stroke, and heart failure. Furthermore, large outcome trials, including the Systolic Hypertension in the Elderly Program (SHEP),[29] the Syst-Eur trial,[7] and the Systolic Hypertension in China (Syst-China) trial,[30] have demonstrated remarkably similar reductions in the risk of stroke and heart failure with effective treatment of isolated hypertension in the elderly. A recent meta-analysis of 8 trials in elderly patients with isolated systolic hypertension that demonstrated a 13% reduction in total mortality, an 18% reduction in CV mortality, a 30% reduction in stroke and a 23% reduction in coronary events, provides further compelling evidence to support the aggressive treatment of these patients.[31]

Widened pulse pressure adds further risk to patients with elevated diastolic or mean arterial pressure with respect to cerebrovascular events.[32] This includes analyses of the Framingham database.[33] Widened pulse pressure increases mechanical stretch on the arteries and may hasten the development of intimal damage that leads to both atherosclerosis and thrombotic events. Elevated systolic pressure may increase left ventricular mass, predisposes to heart failure, and increases oxygen demand. Reduced diastolic pressure, on the other hand, may reduce coronary perfusion pressure and predispose to myocardial ischemia.[34] A recent analysis from the SHEP study demonstrated a 11% increase in the risk of stroke and a 16% increase in the risk of all-cause mortality for every 10 mm Hg increase in pulse pressure. Thus, increased conduit vessel stiffness is an independent risk factor associated with the risk of cerebrovascular disease.

In addition to BP readings obtained in the office or clinic setting, recent data from outcome studies suggest that 24-hour and nocturnal systolic pressure and 24-hour pulse pressure are superior indicators of CV risk. In the Syst-Eur study, both 24-hour systolic pressure and the night-to-day systolic BP ratio were powerful and independent predictors for stroke.[35] In an Italian Study (PIUMA), ambulatory pulse pressure was a stronger predictor of risk than office pulse pressure.[36]

While pulse pressure has evolved to be a strong predictor of CV risk, evidence for its usefulness in clinical practice is still very limited. Indeed, unlike systolic BP, there are virtually no data on the impact of therapeutically narrowing pulse pressure on clinical outcomes. Furthermore, there is no frame of reference for what level of widened pulse pressure should be taken into serious clinical consideration or when therapeutic intervention should be introduced. Accordingly, until treatment outcome data are available for pulse pressure, physicians should focus on reducing systolic BP and not on whether raising diastolic pressure will decrease risk.

Hypertension and endothelial dysfunction: causes, consequences, and clinical corollaries

The endothelium plays an important role in regulation of vascular wall homeostasis.[37,38] It also exerts effects on formed elements in the blood stream including leukocytes, platelets, and coagulation factors. Vascular wall homeostasis is maintained via the production of vasorelaxants such as nitric oxide (NO), prostacyclin I_2, C-type natriuretic peptide, and various endothelium-derived hyperpolarizing factors (ie, cytochrome P-450 products), and vasoconstrictors (ie, endothelin-1 [ET-1] and endothelium-derived contracting factor [EDCF], including cyclooxygenase products like endoperoxides and thromboxanes). As one ages, the endothelium becomes dysfunctional under the influence of CV risk factors like hypertension, hyperlipidemia, or smoking, and in the presence of atherosclerosis or diabetes.

Increased oxidative stress in the vascular wall is one of the mechanisms leading to endothelial dysfunction. It results in the breakdown of NO and enhanced production of ET-1 and EDCF, leading to vasospasm.[39] ET-1 also stimulates smooth muscle cell migration and – with increased oxidation of low density lipoprotein cholesterol, upregulation of monocyte chemotactic protein-1, and increased inflammation of vessel wall – contributes to the progression of atherosclerosis. On the other hand, upregulation of adhesion molecules and plasminogen activator inhibitor-1 creates a prothrombotic state. In this setting, an unstable plaque with a thin fibrous cap may rupture, resulting in coronary artery occlusion. A recent study has associated, for the first time, endothelial dysfunction with increased risk of CV events, including MIs and heart failure.[40]

There has recently been great interest in determining whether it is feasible to improve endothelial function pharmacologically. Experimentally, ACEIs and CCBs have been shown to regress some of the structural changes in blood vessels described above, resulting in improved endothelial function.[41] ACEIs, AT_1 receptor antagonists and CCBs have all been shown to improve endothelial function better than ß-blockers in patients with essential hypertension.[42-45] In these patients, treatment with a CCB resulted in improved structure and endothelium-dependent relaxation in small arteries obtained from gluteal subcutaneous biopsies; however, these structural and functional changes were not observed in patients treated with atenolol, despite an equal reduction in BP.[45] It remains to be seen whether small arteries from other vascular beds may benefit from therapy and whether improvement of endothelial function results in better clinical outcomes in patients with hypertension.

Atherosclerosis trial update: current perspectives and clinical challenges

The main pharmacologic strategy in the primary and secondary prevention of atherosclerosis, especially coronary heart disease (CHD), has involved the use of lipid-lowering agents.[46-49] Recent evidence suggests that other classes of agents may also afford protection from CV events. Because the renin-angiotensin system is known to play a pathophysiologic role in atherosclerosis,[50] several trials have assessed the impact of ACEIs on various abnormalities associated with atherosclerosis.

• The Trial on Reversing Endothelial Dysfunction (TREND), a substudy of the Quinapril Ischemic Event Trial (QUIET), demonstrated the ability of an ACEI to reverse endothelial dysfunction by 22%, as assessed by the response to acetylcholine.[51] It should be noted, however, that these patients were undergoing percutaneous coronary intervention and were potentially at high risk for CV events. Indeed, earlier studies that examined the impact of ACEIs on outcomes had shown a neutral result.

• The recent Heart Outcomes Prevention Evaluation (HOPE) study demonstrated a ~20% reduction in mortality and CV events in over 9000 patients at high risk for vascular events.[11]

• Another promising approach to influence atherosclerosis is the use of CCBs. The International Nifedipine Trial on Antiatherosclerotic Therapy (INTACT), conducted in Europe, demonstrated that the dihydropyridine CCB nifedipine had a neutral effect on the regression of atherosclerotic lesions on angiography, but a significant reduction in the development of new lesions and progression of disease.[52]

• Similar results were obtained from a study conducted at the Montreal Heart Institute using nicardipine, another dihydropyridine CCB. Both this study and the one above did not show any changes in clinical outcomes.

• The Prospective Randomized Evaluation of the Vascular Events of Norvasc Trial (PREVENT) was designed to test the hypothesis that amlodipine might exert a beneficial effect on new coronary lesion formation or atherosclerosis regression in 800 patients with coronary artery disease.[53] Amlodipine is a third-generation dihydropyridine CCB with unique effects on cardiac and vascular cell membranes, including antioxidant and membrane stabilizing effects and the release of nitric oxide.[54,55] In PREVENT, none of the patients had heart failure and diabetes. Amlodipine had no significant effect on coronary lesions as determined by quantitative coronary angiography (QCA), the primary outcome of the trial. However, significant reduction in carotid intimal-medial thickness, as demonstrated by sonography, was observed. In addition, there was a significant reduction in hospitalization for unstable angina, as well as the need for revascularization procedures.

Ongoing studies will expand due to the encouraging results of HOPE and PREVENT by employing newer imaging techniques such as intravascular ultrasound (IVUS) to enhance visualization of the coronary arterial tree and allow for better detection of atherosclerotic progression or regression with various classes of agents.

• The REVERSAL study, inspired by the results of the AVERT study,[56] will compare the effect of atorvastatin versus pravastatin on coronary lesions determined by IVUS and QCA on 600 patients.

• Results of the ALLHAT and PEACE studies[57,58] will hopefully extend the findings of the beneficial effects of ACEI from the HOPE study to patients at lower risk.

• Last but not least, the CAMELOT/NORMALISE study will compared the effects of the CCB amlodipine, ACEI enalapril, and "usual care" on clinical events as well as coronary atherosclerotic progression as determined by IVUS.

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