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 INSIGHT Trial: New Evidence on Cardiovascular Protection

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Satellite Symposium at the 10th European Society of Hypertension Scientific Meeting

Gothenborg, Sweden June 3, 2000

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Antihypertensive drug therapy can result in a substantial reduction in cardiovascular mortality and morbidity for both younger and older patients over a wide range of pre-treatment blood pressures. A decision to initiate antihypertensive treatment is usually dependent on the severity of blood pressure elevation and the presence of risk factors for cardiovascular disease. The 1999 WHO-ISH Guidelines recommend the assessment of the global cardiovascular risk of the hypertensive patient having a cardiovascular event in the subsequent 10 years.[1] Concomitant risk factors for cardiovascular disease, such as hypercholesterolemia, diabetes, smoking, a family history of premature coronary artery disease (CAD), and left ventricular hypertrophy are more common in hypertensive than in normotensive subjects, and result in an overall risk greater than the sum of the individual risks. In higher risk patients, there is need for strict blood pressure control to optimize outcomes, especially in patients with diabetes as demonstrated in the HOT[2] and UKPDS[3] studies. To achieve these goals requires anti-hypertensive agents that are effective, well tolerated, and do not result in metabolic disturbances that could theoretically be counter-productive.

Many questions remain regarding the application of antihypertensive treatment in patients at increased risk of cardiovascular morbidity. Until recently, most hypertension trials have not taken coexisting risk factors and established cardiovascular disease into account. Few studies have addressed whether antihypertensive therapy influences outcome in patients with symptomatic coronary and cerebrovascular disease. However, recent studies have started to evaluate whether the range of antihypertensive agents available today have different effects on outcomes in higher risk patients. What are the benefits with the newer agents (ie, the calcium channel antagonists, angiotensin converting enzyme [ACE] inhibitors, and angiotensin receptor blockers) in comparison with the older agents (diuretics and beta-adrenergic blockers) that were used in many of the original placebo-controlled outcome trials? Is the agent most effective in reducing blood pressure, at the worst, not inferior to alternative medications on long-term outcome. Are the newer agents better tolerated, do they improve patient compliance, and do they result in better blood pressure control? Do the newer agents have properties that might limit target organ damage caused by hypertension in addition to their blood pressure lowering effect?

Comparison between antihypertensive agents on cardiovascular outcomes

Although at least 16 major placebo-controlled studies have demonstrated the beneficial effects of antihypertensive treatment on cardiovascular event rates, there are few studies that have directly compared one agent with another. A recent meta-analysis of 8 placebo-controlled treatment trials in systolic hypertension included 15,693 patients.[4] Antihypertensive treatment reduced all-cause mortality by 13%, cardiovascular

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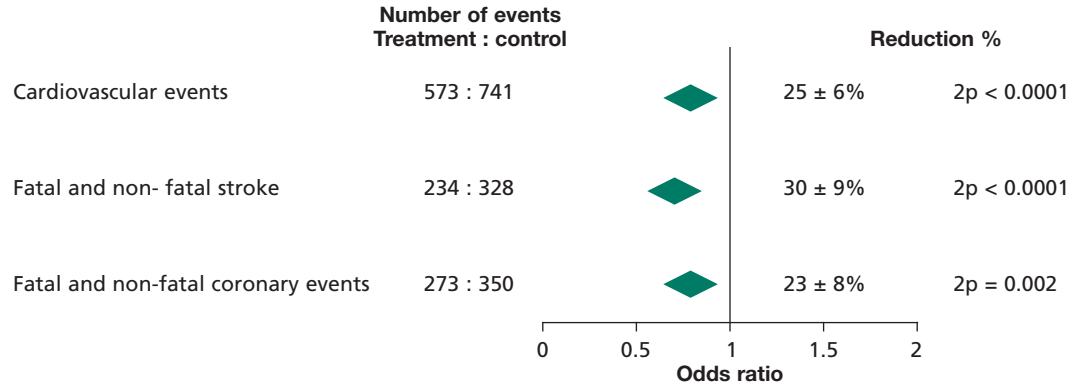
The topics presented in *Cardiology Scientific Update* are independently determined and the content authored exclusively by physician-members of the Division of Cardiology, St. Michael's Hospital. *Cardiology Scientific Update* is made possible by unrestricted funding from the publisher, Snell Medical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

Figure 1: The benefits of antihypertensive treatment in patients with systolic hypertension: A summary of 7 randomized controlled trials.[4]



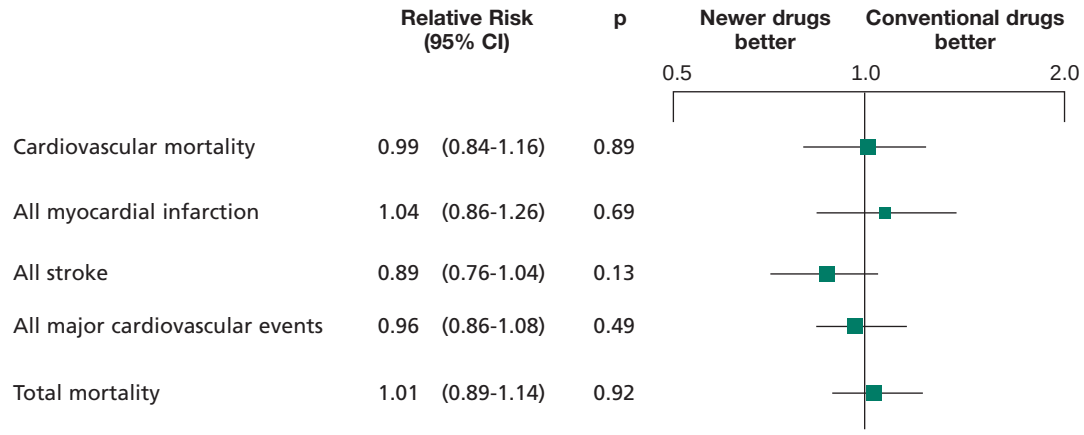
mortality by 18%, cardiovascular complications by 26%, stroke by 30% and coronary events by 23% (Figure 1).

In contrast, randomized control trials that have attempted to show differences in cardiovascular outcomes between antihypertensive agents have so far failed to demonstrate that one agent is superior to another. The STOP 2 trial (Swedish Trial in Older Patients with hypertension-2 study)[5] compared conventional (atenolol, metoprolol, or a hydrochlorothiazide/ amiloride combination) with newer treatment (enalapril, lisinopril, felodipine, or isradipine) in an open-labelled study of 6614 older patients, aged 70-84 years.[6] The conventional treatment and the newer treatments resulted in an identical blood pressure lowering effect of 35 mm Hg for systolic and 17 mm Hg for diastolic blood pressures.

To achieve the target blood pressure of <160/95 mm Hg, over 46% of the patients required more than one medication, and only 60-66% of patients were taking their randomized medication at the final assessment. The primary endpoint of fatal stroke, fatal myocardial infarction (MI) or other cardiovascular fatality occurred in 221 of 2213 conventionally treated patients (19.8 events/1000 patients), and in 438 of 4401 patients receiving the newer treatment (19.8 events/1000). Although differences in the point estimate of the primary outcome is small between the two treatment groups, the confidence intervals are wide, (Figure 2), and a difference of 15-20% between the two treatment groups may be present.

Secondary analyses suggested that MI and heart failure occurred less frequently in patients treated with ACE

Figure 2: A comparison of conventional (atenolol, metoprolol, or hydrochlorothiazide/amiloride combination) with newer treatment (enalapril, lisinopril, felodipine, or isradipine) on outcomes in patients with hypertension (STOP 2 Hypertension Trial).[5] There were no significant differences between conventional and newer treatments



inhibitors compared to those receiving calcium channel blockers; (relative risk [95% confidence intervals] ACE inhibitors vs calcium channel blockers: MI 0.77 (CI, 0.64-0.96) p=0.018; frequency of heart failure 0.76 (CI, 0.69-0.97) p=0.0025). However, the limitations of the open label and complex study design do not allow a high degree of confidence in this observation.

The STOP 2 study showed that within the limits of the sample size and event rates, similar reductions in blood pressure resulted in no demonstrable difference in the incidence of fatal stroke, fatal MI, or cardiovascular death in patients receiving conventional treatment with diuretics and beta-adrenergic blockers compared to those treated with either calcium channel blockers or ACE inhibitors.

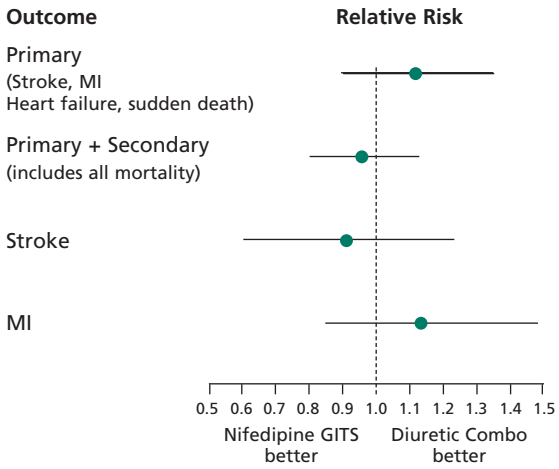
The INSIGHT Trial

The results from the INSIGHT Trial (International Nifedipine once daily Study Intervention as a Goal in Hypertensive Treatment) were presented for the first time at the 10th European Meeting on Hypertension in Gothenborg, Sweden on June 2, 2000. This trial is the first randomized, double-blind study to compare outcomes with a long-acting calcium antagonist used for the treatment of hypertension with a standard conventional approach using diuretics as the initial treatment. It not only permitted an unbiased assessment of the clinical benefit, but also a comparison of anti-hypertensive efficacy, tolerability, and safety. The 6321 patients randomized into the study:

- were aged 65 ± 6.7 years (entry range 55-80 years)
- 53% were female
- had blood pressure greater than 150/95 mm Hg (173 ± 14 / 99 ± 8)
- 23.7% had isolated systolic hypertension (>160 mm Hg systolic, <95 mm Hg diastolic)
- 87% had previously received treatment.

All of the patients had at least one additional risk factor for cardiovascular disease, with hypercholesterolemia (52%), smoking (28%), family history of premature cardiovascular events (21%), and diabetes (20%) being the most frequent risk factors. The patients were randomized to a treatment algorithm that started with either nifedipine GITS 30 mg daily or hydrochlorothiazide 25 mg/amiloride 5 mg. The titration steps to achieve a target blood pressure that was <140/85 mm Hg allowed for an increase in the dose of nifedipine GITS to 60 mg daily and hydrochlorothiazide to 50 mg with the addition of amiloride 5 mg. Subsequently, in both arms of the study, atenolol 25 to 50 mg was added.

Figure 3: INSIGHT Trial: A comparison of nifedipine GITS with diuretic combination in hypertensive patients at higher risk of adverse outcome



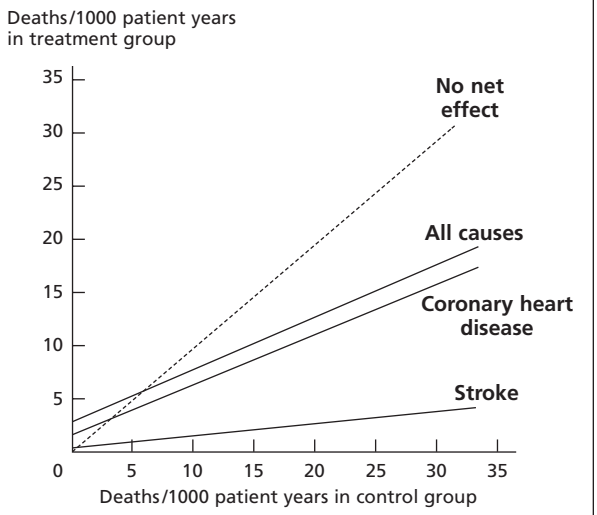
Finally, if the target blood pressure reduction was not achieved, open label antihypertensive treatment of the physician's choice could be added.

The blood pressure at entry into the study was 176/99 mm Hg in both treatment groups. Patients in both the nifedipine GITS and the diuretic combination groups achieved identical and sustained blood pressure lowering to 138/82 mm Hg throughout the four years of the study. After titration, 71% of patients were managed with one drug alone, and 90% of these patients remained on the initial monotherapy throughout the study. There was no significant difference in primary outcomes between the two treatment groups for the combined endpoint of stroke, MI, heart failure, and sudden death; or the combined primary and secondary endpoints (which included total mortality) (Figure 3). Hyperglycemia and new onset diabetes, as well as both hyperuricemia and gout, were significantly more frequent in patients in the diuretic combination group. However, side-effects such as headache and peripheral edema were reported more often in patients receiving nifedipine GITS. Renal function, as measured by the estimated glomerular filtration rate, was significantly reduced in patients receiving the diuretic combination.

Are there differences between "conventional" and newer antihypertensive agents?

The INSIGHT and the STOP 2 studies were designed as superiority trials to show a 25% difference in primary outcome between the medication arms. Before completion of

Figure 4: A summary of the results of meta-analysis of trials in mild to moderate hypertensive middle aged patients.[6] Although the effect of treatment on the prevention of stroke does not appear to be dependent on baseline risk, the prevention of all-cause mortality and coronary heart disease mortality is only apparent at higher levels of baseline risk.



the study and disclosure of the blinding in the INSIGHT Trial, a decision was made to perform a secondary analysis as a non-inferiority trial. Although no statistical difference was demonstrable for either the primary or secondary endpoints, both trials failed to detect a relative risk difference of 25% between the treatment groups.

Is a 25% difference between treatments important? In a condition as common as hypertension, a 15-20% reduction (or increase) in events, especially in a higher risk population, could translate into a very large number of events.

Summary

Conclusions have been drawn from both STOP 2 and INSIGHT that reduction in blood pressure is the most important factor and that the choice of medication is unimportant. Neither of these trials was designed to show equivalence between the treatment groups and due to the relatively small number of endpoints, future trials would need to capture at least 1000 events to detect a 15% difference in treatments. As such, massive trials are unlikely. We shall depend on combined analyses such as the WHO-ISH blood pressure lowering treatment trialists collaboration. This project, with 37 trials, 270,000 patients followed for 4.3 years, and more than 1 million patient years, will be associated with 30,000 cardiovascular events. Using this database may provide sufficient statistical power to demonstrate important differences in event rates for patients receiving the individual classes of anti-hypertensive agents.

Until this information is available, consideration must be given to a risk structured management of hypertension. It remains possible that antihypertensive treatment given to patients with a risk below a certain threshold will have no effect on outcome, or may even increase mortality from all causes and coronary heart disease[6] (Figure 4). At higher levels of risk (eg, with one or more risk factors as in the INSIGHT trial), the benefits of improved blood pressure control will be dominant. A decision to initiate antihypertensive treatment using the paradigm of the 1999 WHO-ISH guidelines takes into account the overall cardiovascular risk which is not wholly dependent upon the level of baseline blood pressure, resulting in improved cardiovascular protection and outcomes.

References

1. Guidelines Subcommittee. 1999 World Health Organization/International Society of Hypertension Guidelines for the management of hypertension. *J Hypertens* 1999:17:151-83.
2. Hansson L, Zanchetti A, Carruthers SG, et al, for the HOT Study group. Effects of intensive blood pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal treatment (HOT) randomized trial. *Lancet* 1998;351(9118): 1755-1762.
3. UK prospective diabetes study group.Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes. UKPDS 39. *Br Med J* 1998;317:703-713.
4. Staessen JA, Gasowski J, Wang JG, et al. Risks of untreated and treated isolated systolic hypertension in the elderly: metaanalysis of outcome trials. *Lancet* 2000; 355(9207):865-872.
5. Hansson L, Lindholm LH, Ekbom T, et al, for the STOP-Hypertension-2 Study Group. Randomised trial of old and new antihypertensive drugs in elderly patients: cardiovascular mortality and morbidity: the Swedish Trial in Old Patients with hypertension-2 study. *Lancet* 1999:354:1751-1756.
6. Hoes AW, Grobbee DE, Lubsen J. Does drug treatment improve survival? Reconciling the trials in mild-to-moderate hypertension. *J Hypertens* 1995;13:805-811.