



Editorial

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Randomized clinical trials of antihypertensive drugs: All that glitters is not gold

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The Canadian Cozaar Hyzaar Amlodipine Trial (CCHAT), the results of which are reported by Drs. Thomas W. Wilson and colleagues in this issue (page 469), was one of the largest randomized clinical trials (RCTs) of antihypertensive drugs ever carried out in Canada. This trial was well performed and fulfilled all of the criteria for internal validity specified by the Evidence-Based Medicine Working Group.¹ Because RCTs are the gold standard for assessing the efficacy of interventions, this might suggest that the CCHAT provides sufficient evidence to support the use of losartan (or amlodipine) for the treatment of hypertension. However, we believe the choice of outcome measures and active comparator limit the clinical applicability of this trial.

The use of continuous surrogate end points such as blood pressure in RCTs has become popular because they permit the demonstration of a statistically significant difference between 2 interventions in a much smaller and shorter term trial than if clinically important outcomes such as stroke, myocardial infarction or death were used. However, this approach is only appropriate if the surrogate end points are valid proxies for clinically important outcomes. As indicated by Prentice,² this implies that the surrogate must both be a correlate of the true clinically important outcome and fully capture all of the effects of treatment on the clinically important outcome.

In the case of hypertension, we know that elevated systolic or diastolic blood pressure is a risk factor for morbidity and death and that lowering blood pressure is associated with reduced risk for cardiovascular events.³ However, the trials demonstrating the benefits of blood pressure reduction randomly assigned patients only to thiazide diuretic or β -blocker therapy versus placebo. Because antihypertensive drugs have multiple effects, it is quite possible that newer agents may have “unintended, unanticipated, and unrecognized mechanisms of action that operate independently of the disease process.”⁴ For example, in the Evaluation Group of Long-Term Antihypertensive Treatment (GLANT) Study — an RCT carried out in Japan that compared the angiotensin-converting enzyme (ACE) inhibitor delapril with the calcium-channel blocker nifedipine or manidipine in 2042 patients with hypertension — patients given a calcium-channel blocker had a higher incidence of stroke at 1 year (risk ratio 3.0, 95% confidence interval 1.1–8.3, $p = 0.02$), despite having greater blood pressure reductions, than the patients given the ACE inhibitor.⁵ Similarly, in the Multicenter Isradipine Diuretic Atherosclerosis Study (MIDAS) — an RCT comparing the calcium-channel blocker isradipine to hydrochlorothiazide in 883 hypertensive patients over 3 years — patients given isradipine had a higher incidence of major vascular events than those given hydrochlorothiazide (5.7% v. 3.2%, $p = 0.07$), although there was no difference between the 2 groups in the reduction of diastolic blood pressure or in the primary outcome variable (a surrogate end point defined by the rate of progression of carotid arterial intimal-medial thickness).⁶ Finally, in the Fosinopril versus Amlodipine Cardiovascular Events Trial (FACET),⁷ both fosinopril and amlodipine were efficacious in lowering blood pressure in 380 hypertensive patients with diabetes; however, patients in the fosinopril group had a sig-



nificantly lower risk of cardiovascular events (risk ratio 0.49, 95% confidence interval 0.26–0.95) than those in the amlodipine group. Thus, we believe that the use of blood pressure lowering as the only measure of efficacy in a short-term antihypertensive trial is not a valid surrogate for the outcomes of primary interest to the clinician and the patient: long-term prevention of stroke, myocardial infarction or death.

The second issue limiting the strength of inference that can be drawn from the CCHAT is the use of amlodipine as an active comparator of losartan. Although new drugs should ideally be evaluated in a placebo-controlled RCT (to allow accurate ascertainment of drug effect over placebo effect), the weight of the evidence from previous studies means that it would now be unethical to carry out a placebo-controlled trial of antihypertensive therapy. Thus, we agree that any new antihypertensive drug must be compared with another active drug. However, this other drug should be one that has been definitively proven to be safe and efficacious in preventing clinically important outcomes (e.g., stroke, myocardial infarction or death). Given the controversy over the safety of dihydropyridine calcium-channel blockers in hypertension,⁸ we question whether amlodipine fulfills this requirement. Although the SYST-EUR Trial⁹ suggests that long-acting dihydropyridines are beneficial in the treatment of hypertension, the definitive answer awaits completion of ongoing long-term trials, such as the Antihypertensive and Lipid-Lowering Treatment for Prevention of Heart Attack Trial (ALL-HAT), that are comparing the various antihypertensive classes for their effects on clinically important outcomes.

As an extension of the above argument, we believe that the safety and quality-of-life data presented in the CCHAT merit further comment. Although we agree with Wilson and colleagues that noncompliance with antihypertensive therapy is an important problem and that efforts should be made to prescribe the best tolerated antihypertensive agents, we are unconvinced that the data on 12-week tolerance and quality of life presented by the CCHAT Study Group are sufficient to justify the widespread use of losartan or amlodipine for hypertension. As the authors allude to, over 50% of current antihypertensive prescriptions are for newer agents (particularly ACE inhibitors and calcium-channel blockers).¹⁰ This practice appears to be driven by the belief that these agents are more efficacious or have fewer side effects than the traditional ones. However, this perception is unsupported by the evidence. In the 3 RCTs that have directly compared drugs from several antihypertensive classes, the newer agents were no more efficacious in lowering blood pressure or any better tolerated than thiazides or β -blockers.^{11–13} In fact, in the 2 placebo-controlled trials, the frequency of side effects reported by patients receiving

antihypertensive therapy (of any class) was similar to that reported by patients given a placebo.^{11,12} Moreover, analyses of the data from the Treatment of Mild Hypertension Study (TOMHS)¹⁴ and the Systolic Hypertension in the Elderly (SHEP) database¹⁵ confirm that low-dose thiazides and β -blockers do not exert significant adverse effects on metabolic parameters over the long term. Finally, long-term quality-of-life data from the TOMHS¹⁶ confirmed the findings of an earlier meta-analysis of 9 studies¹⁷ that hypertensive patients treated with medication have better quality of life than those given placebo. Although differences in quality-of-life measures between groups treated with different antihypertensive drugs were small and of questionable clinical significance, the TOMHS data suggest that patients given a diuretic or β -blocker may even have more improvement in quality of life than those treated with other antihypertensive agents.¹⁶

How then should the clinician incorporate the information from the CCHAT? Although the study does prove that losartan and amlodipine appear to lower blood pressure and have minimal side effects, we believe that the recommendations of the Canadian Hypertension Society still apply — namely, only drugs that have been shown to reduce clinically important outcomes in long-term RCTs (thiazides and β -blockers) should be used as first-line therapy, except in certain well-defined circumstances.

Well-performed, internally valid RCTs may not provide the evidence clinicians need to justify changing practice. Even for gold standards, all that glitters is not gold!

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