

## Putting ACCOMPLISH into context: management of hypertension in 2010

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The much publicized Avoiding Cardiovascular events through COMbination therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial<sup>1</sup> evaluated whether combination therapy with an angiotensin-converting enzyme (ACE) inhibitor (benazepril) and a dihydropyridine calcium channel blocker (amlodipine) was superior to combination therapy with the same ACE inhibitor and a thiazide diuretic (hydrochlorothiazide). Despite a statistically significant result favouring the combination of ACE inhibitor and calcium channel blocker, the clinical implication of this study remains a topic of substantial debate. Some hypertension experts have advocated changing national guidelines on the basis of these results,<sup>2</sup> but others have been more circumspect.<sup>3</sup> Our purpose here is to review the implications of ACCOMPLISH for Canadian clinicians.

ACCOMPLISH enrolled 11 506 individuals over 55 years of age who had hypertension and were at high cardiovascular risk (see Appendix 1, available at [www.cmaj.ca/cgi/content/full/cmaj.092142/DC1](http://www.cmaj.ca/cgi/content/full/cmaj.092142/DC1)). Although 75% of the participants were taking two or more antihypertensive agents before enrollment (and 38% were taking three drugs), blood pressure was uncontrolled (> 140/90 mm Hg) in two-thirds of participants. Patients in both study arms were started on combination therapy and underwent aggressive monthly up-titration to achieve target blood pressure. As a result, systolic blood pressure declined by about 14 mm Hg in both treatment arms. ACCOMPLISH was stopped early because the primary outcome — a composite of cardiovascular events and death — was significantly lower in the group receiving the ACE inhibitor and calcium channel blocker (9.6% v. 11.8% after three years, hazard ratio 0.80, 95% confidence interval [CI] 0.72–0.90). Two-thirds of the primary end points consisted of admissions to hospital for unstable angina or coronary revascularization procedures, which has led some to argue that ACCOMPLISH merely demonstrated that amlodipine reduces anginal symptoms more effectively than a thiazide. Nonetheless, it is worth noting that there was a statistically significant benefit with the combination of ACE inhibitor and calcium channel blocker in terms of “death, nonfatal MI [myocardial infarction], or nonfatal stroke” (5.0% v. 6.3%, hazard ratio 0.79, 95% CI 0.67–0.92). In addition, the prespecified secondary renal outcome of “doubling of serum creatinine or development of end-stage renal disease” was significantly less common among patients treated with ACE inhibitor and calcium channel blocker (2.0% v. 3.7%, hazard ratio 0.52, 95% CI 0.41–0.65).<sup>4</sup>

Was ACCOMPLISH a well-conducted active-control

### Key points

- Most individuals with hypertension need more than one drug to achieve blood pressure targets.
- The low rates of cardiovascular events in both arms of the ACCOMPLISH trial relative to previous antihypertensive trials underscores the importance of prompt control of blood pressure.
- The ACCOMPLISH trial confirmed the benefits of combination therapy for high-risk individuals whose blood pressure is substantially above target.

trial?<sup>5</sup> In a word, yes. The ADVANCE Trial<sup>6</sup> (Appendix 1, available at [www.cmaj.ca/cgi/content/full/cmaj.092142/DC1](http://www.cmaj.ca/cgi/content/full/cmaj.092142/DC1)) had previously proven that a combination of ACE inhibitor and thiazide, akin to the active comparator in ACCOMPLISH, was more efficacious than placebo for a similar patient population. The only methodologic concern with ACCOMPLISH is the fact that it was stopped early. Although this is not necessarily a problem, trials that are stopped early may overestimate treatment effects.<sup>7</sup> This may be particularly relevant to interpreting the reported differences in renal outcomes in ACCOMPLISH. Although fewer patients treated with ACE inhibitor and calcium channel blocker experienced doubling of serum creatinine, ACCOMPLISH was stopped about one year earlier than usual for trials reporting renal outcomes. As such, the initial hemodynamic changes caused by each drug (amlodipine inducing a short-term rise and thiazide diuretics an early drop in glomerular filtration rate) had greater impact on an end point such as measured creatinine than would have been the case if follow-up had not been truncated. Indeed, the rates of decline in glomerular filtration rate after the first three months appeared similar in the two arms of ACCOMPLISH.<sup>8</sup>

The most striking result in ACCOMPLISH was the low rate of cardiovascular events in both arms relative to prior antihypertensive trials. For example, the Antihypertensive and Lipid-

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Lowering treatment to prevent Heart Attack Trial (ALLHAT)<sup>9</sup> enrolled patients of similar age and blood pressure. However, despite lower rates of cardiovascular disease and diabetes mellitus, the event rates in ALLHAT were nearly double those in ACCOMPLISH (Appendix 1, available at [www.cmaj.ca/cgi/content/full/cmaj.092142/DC1](http://www.cmaj.ca/cgi/content/full/cmaj.092142/DC1)). This observation emphasizes the value of achieving control of blood pressure quickly. Although 73% of the ACCOMPLISH participants achieved treatment goals within six months, only 55% of those in ALLHAT met their targets by 12 months, and average systolic blood pressure at one year into the trial was nearly 6 mm Hg higher in ALLHAT than in ACCOMPLISH. Indeed, the rapidity of achieving blood pressure treatment goals has been correlated with long-term prognosis in other hypertension trials, even if differences in blood pressure between patients with immediate and late response disappeared after only a few months.<sup>10</sup> Therein lies the problem for blood pressure treatment based on stepped care, whereby drugs are initiated sequentially with observation for response after each step: most individuals with hypertension need more than one drug to achieve targets. Starting with two drugs may enable the clinician to achieve control of blood pressure more rapidly, but whether the use of fixed-dose combinations improves tolerability, adherence with therapy and cost-effectiveness are unanswered questions that are still under study.

Before deciding on the implications of ACCOMPLISH for Canadian clinicians, three other facts are worthy of comment. First, ACCOMPLISH was not a trial of patients with newly diagnosed, uncomplicated hypertension; rather, it enrolled older individuals at high risk for cardiovascular events in whom initial therapy had already failed. Second, ACCOMPLISH reported a significant difference in clinical outcomes between treatment arms despite minimal differences in blood pressure control. This result contrasts with prior evidence that the most important predictor of outcomes with antihypertensive therapy is the extent to which blood pressure is reduced.<sup>11</sup> It is possible that certain drug combinations may exert different effects and that pharmacogenomics may help to guide the choice of drug combinations in the future, but these hypotheses must be tested. The medical literature provides numerous examples of initially impressive treatment effects that have been found to be smaller (or that have been disproved) in subsequent studies.<sup>12</sup> Therefore, caution is warranted in extrapolating from the first study reporting an unexpected finding. Although the various antihypertensive classes endorsed in the guidelines of the Canadian Hypertension Education Program (ACE inhibitors, angiotensin receptor blockers, calcium channel blockers, thiazides and  $\beta$ -blockers for younger patients) appear equivalent when used as first-line monotherapy,<sup>11</sup> testing different combinations head-to-head is the next frontier in blood pressure trials. Finally, it is important to emphasize that most strokes and myocardial infarctions occur in individuals with systolic blood pressure in the range of 130–150 mm Hg.<sup>13</sup>

What are the implications of ACCOMPLISH? In our opinion, ACCOMPLISH confirms the benefit of combination therapy for high-risk individuals with hypertension and thus supports the recommendation of the Canadian Hypertension Education Program to start combination therapy for patients with systolic blood pressure that is more than 20 mm Hg above

target ([www.hypertension.ca](http://www.hypertension.ca)). Although a combination of ACE inhibitor and calcium channel blocker is appropriate for high-risk patients similar to those enrolled in ACCOMPLISH, clinicians should individualize the choice of which drugs to combine according to patients' particular combinations of comorbidities.

This article has been peer reviewed.

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