Hypertension control in patients with diabetes

In the September 2011 issue of *Canadian Family Physician*, Campbell et al, who are members of the Canadian Hypertension Education Program (CHEP), wrote a review on the management of hypertension in patients with type 2 diabetes.[1] We commend the authors' effort in raising awareness and providing recommendations for clinicians to treat this complex patient population. However, we believe that clinicians should be aware of several controversies that are not adequately discussed in the Campbell et al review. It is our hope that by highlighting some of these controversies, clinicians will be better able to assess potential harms and benefits when managing patients with hypertension and diabetes. We recommend that family doctors take a far more informed approach to blood pressure (BP) management in patients with diabetes, and in all other populations. Simply put, aggressive management is not necessarily better, despite what we are led to believe.

The astounding aspect of the Campbell et al review is the absence of discussion regarding the only randomized controlled trial (RCT) directly relevant to BP control, ACCORD-BP (Action to Control Cardiovascular Risk in Diabetes—Blood Pressure).[2] In ACCORD-BP, there was no benefit seen in the primary outcome between intensive BP control and standard control; however, a 2% absolute risk increase in serious adverse events was seen in the intensive arm. The results of ACCORD-BP were published in 2010; however, the Canadian Diabetes Association and CHEP have yet to comment on it. While it is true that the target systolic BP (SBP) in ACCORD-BP is lower than the current recommendation suggested by Campbell et al, the results of ACCORD-BP are key to a more progressive approach to hypertension management that considers both benefits and harms of drug therapy. Similarly, INVEST (International Verapamil SR–Trandolapril Study) raised concerns regarding aggressive BP lowering in patients with diabetes and coronary artery disease.[3] The INVEST trial was an open-label, blinded-end-point RCT that involved 22 576 patients with hypertension and coronary artery disease. An observational secondary analysis in 6400 patients with diabetes aimed to evaluate the relationship between all-cause mortality and SBP in 3 groups of patients who had SBP of lower than 130 mm Hg, 130 to 139 mm Hg, or higher than 139 mm Hg. The adjusted analysis reported an increased risk of all-cause mortality in the group with SBP lower

than 130 mm Hg versus the group with SBP from 130 to 139 mm Hg (hazard ratio 1.2, 95% CI 1.01 to 1.32). Also, contrary to the suggested benefits of mortality and morbidity reduction, a 2009 Cochrane systematic review (not cited in the Campbell et al review) comparing treatment BP targets (≤135/85 mm Hg vs standard targets between ≤140/90 and ≤160/100 mm Hg) did not show a significant reduction in either overall mortality or total cardiovascular events in patients with diabetes.[4] The results of ACCORD-BP, the INVEST secondary analysis, and the Cochrane review on BP targets certainly raise serious concerns about the advisability of attempting to aggressively lower BP in this population.

How did Campbell et al justify their claims? They cited 3 studies as evidence for their recommendation: the Syst-EUR (Systolic Hypertension in Europe) trial,[5] the HOT (Hypertension Optimal Treatment) trial,[6] and a 2005 meta-analysis.[7] First, the cited 2005 meta-analysis included the UKPDS-38 (UK Prospective Diabetes Study Group) trial.[8] In UKPDS-38, the BP target was lower than 180/105 mm Hg in the control group—a value above the current acceptable range, which therefore limited generalizability to current practice. If one excludes the UKPDS-38 trial, the mortality and morbidity reduction seen in the meta-analysis[8] is no longer observed. Second, Syst-EUR was not designed as a BP target trial, but as a comparison of the first-line calcium channel blocker, nitrendipine, with placebo. Third, the HOT trial, which was used as the basis for the Canadian Diabetes Association and CHEP recommendation of diastolic BP lower than 80 mm Hg, randomized a diverse sample of hypertensive patients to diastolic BP targets of ≤90, ≤85, or ≤80 mm Hg.[6] While a 50% relative risk reduction in serious cardiovascular events was seen in the patients with diabetes, this was a subgroup consisting of only 8% of the randomized population and was likely a chance observation due to the lack of adjustment for multiple statistical comparisons. Thus, the results of the HOT trial should at best be viewed as hypothesis generating; the results require confirmation in a new RCT. Again, this is where ACCORD-BP becomes extremely relevant, as it was an RCT designed to answer the question correctly.

Campbell et al recommend "an ACE [angiotensin-converting enzyme] inhibitor or an ARB [angiotensin receptor blocker] as a potential first-line therapy in all people with hypertension and diabetes."[1] In addition to lowering BP, it has been suggested that renin-angiotensin blockers reduce albuminuria.[1] Albuminuria is a surrogate marker for renal damage and a risk factor for progression to kidney disease. However, despite the proposed superiority of ACE inhibitors in reducing albuminuria, their ability to reduce clinically important renal dysfunction has been contested. A meta-analysis by Casas et al comparing renal outcomes among patients taking ACE inhibitors or ARBs and those taking other antihypertensive drugs failed to show statistically significant differences in the risk of doubling serum creatinine.[9] The investigators did find a statistically significant reduction in end-stage renal disease associated with ACE inhibitors or ARBs (relative risk 0.87, 95% CI 0.75 to 0.99); however, this finding was not robust and was likely due to bias. Casas et al cautioned that the benefits were driven by smaller studies and were not observed in the largest study, ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial).[10] The authors concluded that the beneficial renal effects were likely a result of BP lowering rather than effects due to renin-angiotensin system blockade. Clinicians, therefore, should not feel compelled to prescribe ACE inhibitors to patients with diabetes, as the superiority of their renal protective effects is debatable. Medication tolerability and cost should be an important part of this consideration.

Our final concern is that the Campbell et al article claims to represent a systematic review of all available evidence on this topic. However, despite the mention of a literature search conducted by a Cochrane librarian, no relevant Cochrane reviews were cited.[4,11] Compared with Cochrane reviews, the Campbell et al article lacks transparency on how trials are included or excluded from their analyses. For example, Syst-EUR is cited as evidence for BP targets when the trial was not designed to assess BP targets. Conversely, ACCORD-BP, which was designed to study the efficacy of BP targets in patients with diabetes, was mentioned but not used to inform recommendations. The authors do mention that some of the recommendations were based on expert opinion, but do not mention which recommendations this pertains to; therefore, it is impossible for the reader to make any judgment. Further, this single statement contrasts with the long discussion of a systematic process that they claim to have followed.

In conclusion, despite its adoption by Canadian guidelines, the proposed target SBP of lower than 130 mm Hg has never been tested in an RCT. To our knowledge, there is no study comparing the effects of attempting to achieve an SBP target of lower than 130 mm Hg with attempting to achieve an SBP level lower than 140 mm Hg in patients with diabetes. The recommendation is based on expert consensus, and its value has not been established in a clinical setting. Campbell et al are asking clinicians to treat to a lower SBP target with unproven benefits. A proper harm-benefit analysis must be performed before attempting to reduce BP to below standard targets. In addition, it is important to recognize that hypertension is only one potential modifiable risk factor for macrovascular disease in patients with diabetes. A multifactorial approach involving dietary intervention, regular exercise, smoking cessation, glycemic control, lipid management, and BP control has been shown to reduce mortality and cardiovascular

events.[12,13] Therefore, rather than focusing on a specific risk factor, a holistic approach represents the best way to manage the growing population with diabetes at present.

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Competing interests
None declared

References

1. Campbell NR, Gilbert RE, Leiter LA, Larochelle P, Tobe S, Chockalingam A, et al. Hypertension in people with type 2 diabetes—update on pharmacologic management. *Can Fam Physician* 2011;57:997-1002.
2. Cushman WC, Evans GW, Byington RP, Goff DC Jr, Grimm RH Jr, Cutler JA, et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med* 2010;362(17):1575-85. Epub 2010 Mar 14.
3. Cooper-DeHoff RM, Gong Y, Handberg EM, Bavry AA, Denardo SJ, Bakris GL, et al. Tight blood pressure control and cardiovascular outcomes among hypertensive patients with diabetes and coronary artery disease. *JAMA* 2010;304(1):61-8.
4. Arguedas JA, Perez MI, Wright JM. Treatment blood pressure targets for hypertension. *Cochrane Database Syst Rev* 2009;(3):CD004349.
5. Tuomilehto J, Rastenyte D, Birkenhäger WH, Thijs L, Antikainen R, Bulpitt CJ, et al. Effects of calcium-channel blockade in older patients with diabetes and systolic hypertension. Systolic Hypertension in Europe Trial Investigators. *New Engl J Med* 1999;340(9):677-84.
6. Hansson L, Zanchetti A, Carruthers SG, Dahlöf B, Elmfeldt D, Julius S, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. *Lancet* 1998;351(9118):1755-62.
7. Turnbull F, Neal B, Algert C, Chalmers J, Chapman N, Cutler J, et al. Effects of different blood pressure-lowering regimens on major cardiovascular events in individuals with and without diabetes mellitus: results of prospectively designed overviews of randomized trials. *Arch Intern Med* 2005;165(12):1410-9.
8. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. *BMJ* 1998;317(7160):703-13. Erratum in: *BMJ* 1999;318(7175):29.
9. Casas JP, Chua W, Loukogeorgakis S, Vallance P, Smeeth L, Hingorani AD, et al. Effect of inhibitors of the renin-angiotensin system and other antihypertensive drugs on renal outcomes: systematic review and meta-analysis. *Lancet* 2005;366(9502):2026-33.
10. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002;288(23):2981-97.
11. Wright JM, Musini VM. First-line drugs for hypertension. *Cochrane Database Syst Rev* 2009;(3):CD001841.
12. Gaede P, Lund-Andersen H, Parving H-H, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. *New Engl J Med* 2008;358(6):580-91.
13. Gaede P, Vedel P, Larsen N, Jensen G, Parving H-H, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *New Engl J Med* 2003;348(5):383-93.

Health care expectations in Newfoundland

I just had a chance to read the April 2011 issue of *Canadian Family Physician* and found much to disagree with in the correspondence[1] about the periodic health examination.[2,3] I was particularly incensed by the letter "A British perspective," in which Dr Peter Gray tells of spending a short time in the colony of Newfoundland before