Re: Campbell NRC, Leiter LA, Larochelle P, et al. Hypertension in diabetes: A call to action. Can J Cardiol 2009;25:299-302.

Blood pressure drugs have no mortality benefit in diabetic patients

To the Editor:

We question the following statement in the article by Campbell et al (1): "Treatment of high blood pressure in people with diabetes results in large reductions in death...within a short period of time..." This statement was based on references 2 to 10. However, the first two references (2,3) found no mortality benefit from these angiotensin receptor blockers.

The next reference (4) reported a nonsignificant mortality difference after nine years from "tight blood pressure control". Reference 5 is a subgroup of the Appropriate Blood Pressure Control in Diabetes (ABCD) trial. This trial showed no mortality benefit (P=0.8) from aggressive blood pressure control after 5.3 years, while reference 6 represented the balance of ABCD participants – those with higher baseline blood pressure – and demonstrated borderline significant mortality benefit (the given P=0.037 was erroneous).

The Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial (7) reported P=0.03 for mortality, but 79 diabetic patients would have to take perindopril plus indapamide for five years to postpone the death of one patient (78 representing the number needlessly treated).

The Micro Heart Outcomes Prevention Evaluation (MICRO-HOPE) substudy (8) found a nonsignificant mortality difference emerging after two years on ramipril, and 31 diabetic patients would have to take this drug for 4.5 years to postpone one death. Interestingly, the authors propose that much of the action of this angiotensin-converting enzyme inhibitor may be from mechanisms other than those that lower blood pressure (11).

The Systolic Hypertension in Europe (Syst-Eur) trial (9) reported no significant mortality benefit (P=0.09) from calcium channel blockade after two years. Ominously, the study mentioned potential harm from calcium channel blockers in diabetic patients.

Reference 10 was a meta-analysis of diabetic and nondiabetic patients suffering a total of 17,000 major cardiovascular events. In the diabetic patients, the above angiotensin receptor blocker and angiotensin-converting enzyme inhibitor effects were reflected, but because treatment durations were not given, numbers needed or needlessly treated cannot be calculated.

The authors, therefore, are not supported by evidence when suggesting short-term "major reductions in death", and diabetic patients must be told. What is urgently needed are numbers needed or needlessly treated for individual end points – ie, death, ischemic (nontransient ischemic attack) and hemorrhagic stroke, myocardial infarction, heart and kidney failure and microangiopathies – for each of the available blood pressure drugs, for one to five years of treatment, rather than 'relative combined end point risk reductions' without defined treatment periods.

With such numbers needed or needlessly treated (and it is likely that none of them are less than 100 patient treatment-years per end point, which in itself, would make clinical relevance doubtful), we can clearly inform patients and consider other avenues to tackle diabetes, which, after all, is mostly a preventable metabolic disease (insulin resistance secondary to excess visceral fat due to junk food addiction) and of which blood pressure can be a symptom but not the cause.

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Confirming the critical importance of blood pressure control in people with diabetes

From the Authors:

Clinicians are strongly encouraged to redouble efforts to control blood pressure to lower than 130/80 mmHg in people with diabetes. Vos et al question the validity of the evidence for our 'Call to Action'. On the contrary, the 'Call to Action' is supported by strong clinical trial evidence, backed by major national health care organizations and based on an ongoing clinical care gap demonstrated in Canada (1,2). The original 'Call to Action' appropriately referenced evidence from a meta-analysis of randomized controlled clinical trials that documented the large reduction in death and disability that occurs over a short time period, and also referenced individual randomized controlled trials (1). Canadians with diabetes are at twice the risk of death compared with those without diabetes, are at three, seven and 23 times the risk of hospitalization for cardiovascular

disease, chronic kidney disease and lower-leg amputation, respectively, and represent a large disease burden in Canada (3).

Vos et al focus on total mortality, while many of the trials cited, due to size and duration, were not designed to examine changes in total mortality rates. Although the meta-analysis and larger trials showed clear and substantive mortality advantages, Vos et al indicate that the cited meta-analysis did not provide the average duration of the individual studies, making it difficult for them to calculate a number needed to treat (NNT) per year. However, NNT is simple and quick to calculate, and the data required for the calculations are generally provided in the original publications. It is concerning that Vos et al selected a few trials to insinuate that blood pressure-lowering treatment is relatively ineffective based on published NNTs. In the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial (4), 78 people were required to be treated for five years to prevent a death, but people with normal blood pressure who were not recommended for blood pressure-lowering treatment in the 'Call to Action' were included. In this worst-case scenario (78 people treated for five years to prevent a death), the worldwide application of the treatment has been estimated to prevent 400,000 deaths per year (4). In the other trial cited by Vos et al (Micro Heart Outcomes Prevention Evaluation [MICRO-HOPE] trial [5]), 31 people with diabetes would need to be treated with a relatively inexpensive therapy for 4.5 years to prevent one death (or extrapolated to 10 years, 14 treated to prevent a death). The NNTs are lower in several of the other trials not selected by Vos et al.

Furthermore, people are concerned about being disabled as well as dying. For every cardiovascular death in Canada, there are four nonfatal cardiovascular events that result in hospitalization (6). The NNTs to prevent cardiovascular disability are therefore very much lower than to prevent death. For example, the NNT with ramipril for 4.5 years in MICRO-HOPE was 15 to prevent one individual from having a cardiovascular death, myocardial infarction, stroke, admission to hospital for heart failure, a revascularization procedure, development of overt nephropathy, laser therapy for retinopathy or renal dialysis. Treatment of hypertension in people with diabetes very substantially reduces disability as well as death.

Vos et al also suggest that the use of calcium channel blockers in the Systolic Hypertension in Europe (Syst-Eur) trial (7) had no mortality benefit and indicate that the study mentioned harm. In direct contrast, in the Syst-Eur trial, being randomly selected for treatment with a long-acting dihydropyridine calcium channel blocker-based therapy reduced cardiovascular mortality (76% reduction, P=0.01), all cardiovascular events (69% reduction, P=0.002) and all strokes (73% reduction, P=0.02). The reductions in total mortality rate (55% reduction, P=0.09, multifactorial adjusted P=0.04) and in cardiac event rate (63% reduction, P=0.06) were not statistically significant. The only harm to the trial participants that was cited in the publication was the higher cardiovascular death and event rates associated with placebo-based treatment. In the Syst-Eur trial, 21 people with diabetes would need to be treated for two years to prevent a cardiovascular death (extrapolated to 10 years, four treated to prevent a cardiovascular death), and 13 people treated to prevent a cardiovascular event (extrapolated to 10 years, two to three people treated to prevent a cardiovascular event). Notably, the calcium channel blocker-based therapy prevented the majority of the fatal and disabling cardiovascular events that occurred in the two-year trial.

Vos et al critique one of the most effective preventive therapies that are available to health care professionals, where much greater implementation is required. Preventing death and disability is a fundamental aspect of health care delivery and a major responsibility for government, health care professional organizations and all health care professionals. While we agree with Vos et al that greater attention to the prevention of hypertension and diabetes is required, the 'Call to Action' addresses the prevention of death and disability in the expanding ranks of those afflicted with diabetes.

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