Risks and benefits of intensive blood pressure lowering in patients with type 2 diabetes

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The debate about appropriate blood pressure targets for patients with hypertension and diabetes is of substantial public health importance because the global burden of diabetes and hypertension is large and continues to increase. In Canada, nearly 1 in 10 adults has diabetes, and the prevalence is expected to double by 2030.[1] As well, 1 in 4 Canadians has high blood pressure, and the age-standardized prevalence of hypertension has increased by 10% over the past decade.[1] The combination of diabetes and hypertension is associated with a 57% increase in the risk of adverse cardiovascular events, including stroke and myocardial infarction.[2] Studies have unequivocally shown that lowering blood pressure is the most effective single intervention to reduce cardiovascular morbidity and mortality.[2–4]

Until recently, international clinical practice guidelines[5,6] almost universally recommended that hypertension in patients with diabetes be treated to a target blood pressure level of less than 130/80 mm Hg (in contrast to < 140/90 mm Hg recommended for patients without diabetes). However, some emerging evidence suggests that lower systolic blood pressure targets may be associated with an increased risk of adverse events, calling into question the appropriateness of this target and prompting further review of the evidence.

In this article, we review the major studies that address target blood pressure levels for patients with diabetes and hypertension. In particular, we summarize the rationale for the current Canadian Hypertension Education Program and Canadian Diabetes Association harmonized clinical practice recommendations, which continue to recommend blood pressure targets of less than 130/80 mm Hg for patients with diabetes.[7] A summary of the evidence used in this review, which comes from randomized controlled trials and meta-analyses, is presented in Box 1.

What is the basis for the blood pressure target of less than 130/80 mm Hg for patients with hypertension and diabetes?

Since 2004, the Canadian Hypertension Education Program has recommended a target blood pressure of less than 130/80 mm Hg.[8] The diastolic target of less than 80 mm Hg is based on 2 randomized trials: the Hypertension Optimal Treatment (HOT) trial[9] and the normotensive Appropriate Blood Pressure Control in Diabetes (ABCD) trial.[10] The Canadian Hypertension Education Program rates this as grade A evidence, because it is based on treat-to-target randomized controlled trial data. Published in 1998, the HOT trial randomly assigned 18 790 individuals with hypertension to 1 of 3 targets for diastolic blood pressure (≤ 90 mm Hg, ≤ 85 mm Hg or ≤ 80 mm Hg).[9] About 1500 participants (8%) had diabetes at baseline; the outcomes among these individuals were reported in a prespecified subgroup analysis. The mean achieved diastolic blood pressure in the 3 groups were 85.2 mm Hg, 83.2 mm Hg and 81.1 mm Hg, respectively. Despite the relatively small absolute differences in mean levels, the risk of a major adverse cardio-

Key points

- The treatment of hypertension in people with diabetes is a highly effective strategy to reduce the risk of cardiovascular disease and vascular complications of diabetes.
- A blood pressure target of less than 130/80 mm Hg is recommended for patients with hypertension and diabetes.
- Intensive reduction of systolic blood pressure reduces the risk of stroke, but it increases the risk of treatment-related adverse events (e.g., syncope, hypotension and bradycardia).
- People with the highest elevations in blood pressure have the most to benefit from any intervention to reduce blood pressure, irrespective of the target.

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vascular event after 3.8 years of follow-up was 2-fold higher (relative risk [RR] 2.06, 95% confidence interval [CI] 1.24–3.44) among those randomly assigned to a diastolic blood pressure of 90 mm Hg or lower (45 events) compared with a diastolic blood pressure of 80 mm Hg or lower (22 events).

The normotensive ABCD trial,[10] published in 2002, randomly assigned 480 people with diabetes and blood pressures of less than 140/90 to either an intensive (lowering diastolic blood pressure by > 10 mm Hg) or moderate (targeting a diastolic blood pressure between 80–90 mm Hg) diastolic blood pressure control strategy over a mean 5.3 year follow-up period. The primary outcome was change in 24-hour urinary creatinine clearance. The mean blood pressure levels achieved over the last 4 years of follow-up were 128/75 mm Hg in the intensive-control arm and 137/81 mm Hg in the moderate-control arm. Although there was no significant difference in the primary outcome of creatinine clearance, the odds of stroke (a prespecified secondary outcome) were significantly higher among those in the moderate-control group than in the intensive-control group (13 v. 4 events, odds ratio [OR] 3.29, 95% CI 1.06–10.25).

The Canadian Hypertension Education Program has assigned a grade C rating to its target recommendation of less than 130 mm Hg systolic blood pressure. Grade C level evidence is based on lower-quality randomized controlled trial data and/or observational data. There is a lack of direct evidence for this target from treat-to-target randomized controlled trials.[11] The systolic target was based partly on data from the ABCD trial, in which a significant reduction in the risk of stroke corresponded to an achieved mean systolic blood pressure of 128 mm Hg. Consideration was, however, also given to the post hoc epidemiologic analysis of the United Kingdom Prospective Diabetes Study (UKPDS 36, n = 3642), which found a strong and independent association between increased systolic blood pressure and the risk of clinically significant events.[12] For each 10 mm Hg increase in systolic blood pressure, a 15% (95% CI 9%–16%) increase in all-cause mortality and a 17% (95% CI 13%–21%) increase in diabetes-related death was observed.

Box 1: Evidence used in this review

The studies used in this review were selected from the searches performed to develop the 2012 Canadian Hypertension Education Program recommendations.[6] A Cochrane Collaboration librarian searched MEDLINE using a highly sensitive search strategy for randomized controlled trials and systematic reviews of trials published up to August 2011 that evaluated cardiovascular outcomes. To ensure that all relevant studies were included, bibliographies of the identified articles were manually searched. (The details of the search strategies and retrieved articles are available on request.) The search was repeated in August 2012 in preparation for the 2013 Canadian Hypertension Education Program's Consensus Conference. The Canadian Hypertension Education Program's diabetes subcommittee (including R.E.G., L.A.L., S.W.T. and D.M.R.) reviewed this evidence and felt that there were insufficient data to prompt a change in the currently recommended targets for systolic and diastolic blood pressure.

Are there any new trials that directly evaluate the systolic blood pressure target of less than 130 mm Hg?

No new evidence is available that directly informs the 130 mm Hg target. However, additional evidence examining intensive blood pressure control for patients with diabetes is available from the Action to Control Cardiovascular Risk in Diabetes–Blood Pressure (ACCORD-BP) randomized controlled trial[13] and 2 recently published meta-analyses of randomized controlled trials.[14,15]

The ACCORD-BP trial, published in 2010 and involving in 4733 people, compared a standard strategy that targeted a systolic blood pressure of less than 140 mm Hg to an intensive strategy that targeted less than 120 mm Hg. After 4.7 years of follow-up, no significant difference was found between the 2 strategies in reducing the primary composite outcome of major adverse cardiovascular events (237 events [2.09%] in the standard-treatment group v. 208 events [1.87%] in the intensive-treatment group).[13]

Four aspects of the ACCORD-BP trial deserve emphasis. First, the event rate in the control group for the primary outcome (a composite of nonfatal myocardial infarction, nonfatal stroke and death from cardiovascular causes) was only half of the expected event rate of 4%; therefore, the study may have been underpowered to truly detect a difference between the strategies.[13]

Second, ACCORD-BP was part of the larger ACCORD trial, in which all 10 251 patients with diabetes and at high-risk of cardiovascular disease were randomly assigned to either an intensive glucose-lowering strategy (with a target glycated hemoglobin of 6.0%) or a standard glucose-lowering strategy (target glycated hemoglobin of 7%–7.5%). Using a 2 × 2 factorial design, patients were randomly assigned to 1 of 2 substudies: to either a lipid comparison (statin plus placebo v. statin plus fenofibrate) or the ACCORD-BP arm. Therefore, of the 4733 people assigned to treatment within the ACCORD-BP trial, 2371 were also receiving an intensive glycemic intervention and 2362 were receiving a standard glycemic intervention. The result of the statistical test for

interaction between the glycemic and blood pressure interventions was 0.08, a p value that is significant when evaluating interactions in factorial trials.[16] Thus, the potential for interaction between the 2 study arms is raised. If interaction was present, analyses would need to be conducted separately within the 2 factorial subgroups, rather than by pooling all of the patients together — and this may result in further loss of power.

Third, the intensive blood pressure lowering strategy was effective in significantly reducing the risk of stroke, a prespecified secondary outcome, by 47% (2.6% v. 1.5%; hazard ratio [HR] 0.53, 95% CI 0.39–0.89) but also increased the risk of serious adverse events (hypotension, bradycardia and hyperkalemia).

Fourth, our current recommendation for a target systolic blood pressure of less than 130 mm Hg was not tested in the ACCORD study. Therefore, this study, if negative, does not provide definitive evidence on the difference in risks and benefits of less than 130 mm Hg systolic blood pressure compared with less than 140 mm Hg.

Since the publication of ACCORD, Bangalore and colleagues[14] and Reboldi and colleagues[15] independently published meta-analyses that summarize the current literature on hypertension management for patients with diabetes. Although these authors used different methodologic approaches to reviewing and summarizing the evidence, both groups sought to document the relative benefits and risks of lower blood pressure targets.

The meta-analysis by Bangalore and colleagues[14] included 13 trials that compared an achieved systolic blood pressure of less than 135 mm Hg to less than 140 mm Hg or that compared an achieved systolic blood pressure of less than 130 mm Hg to less than 140 mm Hg. Trials were eligible for inclusion if they enrolled patients with diabetes or impaired fasting glucose, and the primary outcome was major adverse cardiovascular events including mortality, cardiovascular mortality, myocardial infarction, stroke and heart failure. The authors also examined microvascular events and serious adverse events as secondary outcomes. Compared with an achieved systolic blood pressure of 140 mm Hg, an achieved blood pressure of less than 135 mm Hg was associated with a reduced odds of death (8.2% v. 7.3%; OR 0.87, 95% CI 0.79–0.95). An achieved systolic blood pressure of less than 130 mm Hg also reduced the odds of stroke (1.6% v. 0.82%; OR 0.53, 95% CI 0.38–0.75).[14]

The meta-analysis by Reboldi and colleagues[15] included 31 antihypertensive drugs trials that included patients with diabetes (excluding data for patients with impaired fasting glucose only). The authors performed series of stratified meta-analyses and meta-regression analyses to determine the effect of systolic blood pressure control on myocardial infarction and stroke.[15] Similar to the results reported by Bangalore and colleagues,[14] this analysis found that lower achieved systolic blood pressure was associated with a reduced risk of stroke (RR 0.61, 95 CI 0.48–0.79) but not myocardial infarction (RR 0.87, 95% CI 0.74–1.02). For every 5% reduction in systolic blood pressure, the risk of stroke was reduced by 13% (95% CI 5%–20%).[15] Not surprisingly, they also found that patients with the highest elevations in blood pressure at entry to the trials had the greatest degree of benefit from any blood pressure–lowering interventions. Those in the highest tertiles of systolic blood pressure on entry had an 18% pooled risk reduction for stroke (95% CI 0.71–0.94) and a 15% pooled risk reduction for myocardial infarction (95% CI 0.74–0.98), irrespective of the achieved blood pressure. Thus, moving the systolic blood pressure target for people with diabetes from less than 130 mm Hg to less than 140 mm Hg may result in an increase in strokes.

What are the risks of intensive blood pressure control?

Intensive blood pressure control has been found to increase the risk of adverse events including hypotension, syncope, bradycardia or arrhythmia, hyperkalemia, angioedema, renal failure and end-stage renal disease. In the ACCORD-BP trial, participants assigned to the intensive-control arm experienced 77 of these adverse events, compared with only 30 adverse events in the standard-control arm.[13] The meta-analysis by Bangalore and colleagues[14] extracted and pooled data on serious adverse events across trials and similarly found that those who achieved lower systolic blood pressure levels experienced significantly more adverse events (OR 1.20, 95% CI 1.08–1.32). When the achieved systolic blood pressure was less than 130 mm Hg, the magnitude of risk for adverse events was even greater (OR 1.40, 95% CI 1.19–1.64).[14]

How does this recent evidence affect clinical practice?

Choosing a single systolic blood pressure target that applies to all people with diabetes appears more complex than previously appreciated. Systolic blood pressure lowering appears to primar-

ily reduce the risk of cerebrovascular disease. Additionally, it is important to remember that those with the highest blood pressure levels and those at highest global risk (i.e., with multiple cardiovascular risk factors) derive the most benefit from reducing blood pressure. Accordingly, a decrease from 140 mm Hg to 130 mm Hg in a person with recent-onset diabetes, no target-organ damage and no other vascular risk factors would have a comparatively lower effect in terms of cardiovascular risk reduction.

People with hypertension and diabetes who can achieve a systolic blood pressure of less than 130 mm Hg may have better outcomes than those that do not achieve this target. However, intensive blood pressure reduction represents a trade-off between stroke reduction and an increased risk of drug-related adverse effects. From a purely mathematical perspective, the risk of an adverse event appears roughly equal to the degree of benefit achieved in terms of reduction in the risk of stroke. However, stroke is generally considered to be a more debilitating and a less reversible outcome than many of the adverse effects that occurred in the ACCORD-BP trial (e.g., hypotension, syncope and bradycardia).[13]

The available meta-analyses[14,15] are limited in that they focus on achieved systolic blood pressure levels rather than a priori protocol-specified systolic blood pressure targets. It is possible, and indeed probable, that patients who are able to achieve lower systolic blood pressure have characteristics that are associated with better vascular outcomes, independent of their blood pressure.

The ACCORD trial[13] raised the potential for interaction between glycemic control and systolic blood pressure reduction, in that the efficacy of blood pressure lowering may also depend on the degree of glycemic control. Because the meta-analyses[14,15] did not control for differences in the duration of diabetes or degree of glycemic control achieved, the relative contributions of glycemic control and systolic blood pressure reduction to risk reduction seen in these studies is unclear .

After considering the pre-ACCORD-BP evidence, the results of the ACCORD-BP trial[13] and the 2 subsequently published meta-analyses,[14,15] most (> 80%) of the Canadian Hypertension Education Program's Recommendations Task Force, which included representatives from the Canadian Diabetes Association subcommittee on hypertension, voted to maintain the target of 130/80 mm Hg. In addition to the above factors considered in making this decision, the effect of diabetes and hypertension on a population-wide level was also considered. Achieving population-level reductions in stroke was deemed a critically important objective, and on the balance, stroke prevention was felt to outweigh the increased risk of drug-related adverse events.

As with all guideline recommendations, we recommend that care providers use their clinical judgment when applying recommendations to individual patients, particularly in the very elderly (aged 80 yr), considering the trade offs of risks and benefits, patient preferences and individual clinical profiles when making treatment decisions.[17] This systolic blood pressure target recommendation remains a grade C recommendation, reflecting the evidence discussed above. Although the systolic blood pressure target recommended by the Canadian Hypertension Education Program differs from that of the European Society for Hypertension and the American Diabetes Association, which both recommend a target systolic blood pressure of less than 140 mm Hg, the evidence synthesis among groups has been similar. Both groups recognize that there are potential cerebrovascular benefits to be gained from lower systolic targets and acknowledge the limitations of the ACCORD-BP trial[13] in identifying a clear systolic target. These issues were addressed differently by each group, with the European Society for Hypertension recommending a systolic target "well below 140 mm Hg,"[6] suggesting that targets below 140 mm Hg are beneficial but that lower targets may be appropriate for certain individuals. Similarly, the American Diabetes Association provides a grade B recommendation for a systolic blood pressure target less than 140 mm Hg, but it also provides a grade C recommendation for a target of less than 130 mm Hg "if it can be achieved without undue treatment burden."[5]

There is still uncertainty about optimal blood pressure targets. The Canadian Hypertension Education Program, in collaboration with the Canadian Diabetes Association, will continue to review the evidence annually and revise our recommendations as new evidence emerges.

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