Can J Diabetes 42 (2018) S186–S189

Contents lists available at ScienceDirect

Canadian Journal of Diabetes

journal homepage: www.canadianjournalofdiabetes.com

2018 Clinical Practice Guidelines

Treatment of Hypertension

Diabetes Canada Clinical Practice Guidelines Expert Committee

Sheldon W. Tobe MD, FRCPC, Richard E. Gilbert MBBS, PhD, FRCPC, Charlotte Jones MD, PhD, FRCPC, Lawrence A. Leiter MD, FRCPC, FACP, FACE, FAHA, Ally P.H. Prebtani MD, FRCPC, Vincent Woo MD, FRCPC

KEY MESSAGES

- People with diabetes should be treated to achieve a BP <130/80 mmHg.
- For persons with cardiovascular disease or chronic kidney disease, including albuminuria, or with cardiovascular risk factors in addition to diabetes and hypertension, an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker is recommended as initial therapy.
- Healthy behaviour interventions are supplementary to pharmacologic therapy and consist of reducing excess body weight, reducing sodium intake toward (2,000 mg/day), increasing consumption of fruits and vegetables (8 to 10 servings per day), low-fat dairy products (2 to 3 servings per day), avoiding excessive alcohol consumption (no more than 2 servings per day in men and no more than 1 serving per day in women) and increasing physical activity levels.
- Most people with diabetes should receive standard-dose monotherapy for initial management of hypertension; however, there is emerging evidence for supporting earlier use of single pill combination therapy.

KEY MESSAGES FOR PEOPLE WITH DIABETES

- It is important to have your blood pressure checked regularly.
- Have your blood pressure checked at least once every year by a health-care provider or more often if your blood pressure is high.
- You can also check your blood pressure at home. If home blood pressure readings are done properly, they may reflect your usual blood pressure more than those done in the health-care provider's office.
- For most people with diabetes, blood pressure should be less than 130/80 mmHg.
- Patient resources on hypertension are available at Hypertension Canada (http://guidelines.hypertension.ca/patient-resources/).

Introduction

Observational and randomized clinical trials and observational data show a strong association between raised systolic and diastolic blood pressures (BPs) and clinically important microvascular (e.g. retinopathy and nephropathy) and cardiovascular (CV) complications in people with hypertension who have diabetes mellitus. The association between BP level (systolic and diastolic) and CV risk is continuous and graded in people with diabetes. Treatment of hypertension appears to confer greater benefits in people with diabetes than in age-matched people with hypertension who do not have diabetes (1–3). The benefits of intensive BP lowering may even exceed those of intensive glycemic control in people with diabetes mellitus for the prevention of CV complications (4,5). Because cardiovascular disease (CVD) is the most common cause of death in people with diabetes mellitus (6), BP control is paramount.

Blood Pressure Targets

In participants with diabetes, there is randomized clinical trial evidence supporting lower BP levels (2 major trials are the United Kingdom Prospective Diabetes Study Group (UKPDS)-38 trial and the Hypertension Optimal Treatment (HOT) trial) (4,7). In the UKPDS-38 trial, more intensive BP lowering led to reductions in risk of microvascular diabetic endpoints of 37% (95% confidence interval [CI] 11–56) and in stroke of 44% (95% CI 11–65) (4). In the treat-to-target HOT trial, within the a priori-specified subgroup of people with diabetes, the rate of major CV events was 51% lower in participants randomly assigned to achieve target BPs <80 mmHg than in subjects with target pressures of 85 to 90 mmHg (7). Therefore, the HOT trial results support a diastolic BP treatment goal of ≤80 mmHg.

Use of combination therapy is supported by the results of the BP-lowering arm of the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial (8). In this trial, 11,140 participants with type 2 diabetes >55 years of age with a history of major CVD or CV risk factors were randomly assigned to receive perindopril/indapamide vs. placebo in addition to current antihypertensive therapy (8). After a mean follow-up period of 4.3 years, combination therapy was associated with a 5.6/2.2 mmHg greater reduction in BP compared with placebo. There were no significant differences in the CV or microvascular primary endpoints between combination therapy and placebo. In the secondary endpoint analysis, however, combination therapy was associated with a significant reduction in CV death (hazard ratio [HR] 0.82, 95% CI 0.68–0.98, p=0.03) and total mortality (HR 0.86, 95% CI 0.75–0.98, p=0.03) compared with placebo. Rates of serious adverse events and permanent discontinuation for hypotension or dizziness were similarly low in combination and placebo groups. Several trials in people without diabetes also found combination therapy to be associated with greater BP lowering, reduced rates of CV endpoints and low rates of adverse events (9,10). Given the significantly greater BP reductions associated with combination therapy, a combination of 2 first-line agents should be used

Conflict of interest statements can be found on page S188.

https://doi.org/10.1016/j.jcjd.2017.10.011

in people with significant elevations in BP. Caution, however, should be exercised in people in whom a substantial fall in BP is more likely to occur or is more poorly tolerated (e.g. the elderly, people with active CAD and people with autonomic neuropathy).

The recommendation to lower systolic BP to <130 mmHg is partly based on prospective cohort data; specifically, the Pittsburgh Epidemiology of Diabetes Complications Study (in people with type 1 diabetes mellitus) and the UKPDS-36 (in people with type 2 diabetes) demonstrated a linear relationship between systolic BP levels and mortality, CAD, overt diabetic nephropathy and proliferative retinopathy (11,12). These associations were maintained even after adjustment for other confounding factors (such as lipid levels, age, sex and glycemic control). In these studies, direct relationships were seen between the magnitude of incremental BP reduction and reductions in risk of hypertension-related complications, over time.

Recent studies have led a re-evaluation of the systolic BP target of 130 mmHg. To a large extent, this has been precipitated by the findings of the Action to Control Cardiovascular Risk in Diabetes-Blood Pressure (ACCORD BP) trial in 2010 which compared the effects of targeting a systolic BP <140 mmHg with that of <120 mmHg (13). The primary outcome, a composite of myocardial infarction (MI), stroke and CV death was neutral, showing no significant difference between the 2 BP groups. These findings and the occurrence of more adverse effects in the lower target group, prompted guideline groups in the United States and Europe to move their threshold for initiation of antihypertensive therapy from 130 mmHg to 140 mmHg (14,15).

On further scrutiny, as noted in a review on the subject by Hypertension Canada and Diabetes Canada (16), the findings of the ACCORD BP trial are not quite as clear-cut as they seem at first glance. Notably, while the primary endpoint was neutral, stroke, a prespecified outcome in ACCORD BP, was reduced by 41% in the group with a <120 mmHg target (13). In addition, ACCORD BP may well have been underpowered, accruing an event rate that was only half of that anticipated. Moreover, a factorial designed study, such as ACCORD, assumes the absence of interaction between its interventions where $p<0.1$ is viewed as statistically significant (17). Notably, the probability of interaction between the glycemia and BP interventions in ACCORD BP was $p=0.08$, suggesting that the response to BP lowering may have been different between those randomized to usual vs. intensive glycemic control.

In the years that followed, the disclosure of the ACCORD BP findings, several meta-analyses and systematic reviews exploring BP thresholds and targets in diabetes have been published (18–21). In general, these concluded that there was little, if any, additional reduction in cardiac events by achieving systolic BP <140 mmHg. While one of these meta-analyses reported an association with CV death and the initiation of antihypertensive therapy in individuals with systolic BP <140 mmHg (21), this was not seen in the other analyses (18–20).

Although far less common than MI, but with devastating effects that make it especially feared by people, it may be argued that stroke warrants separate consideration. In addition to the ACCORD BP study that showed substantial stroke reduction with lower systolic BP (13), the meta-analyses detailed above also showed that while the other components of major adverse cardiac events were not improved, lowering BP <130 mmHg conferred additional protection against stroke (18–21).

Finally, although the Systolic Blood Pressure Intervention Trial (SPRINT) (22) and ACCORD BP (13) were different in their study of individuals without, and with, diabetes, respectively, they each examined similar BP targets in those at high CV risk. As such, it has been reasoned that they might be considered together rather than separately, arguing that a lower systolic BP target is appropriate in high-risk individuals whether they have diabetes or not (23). Taking all these factors into consideration, it is felt that there are insufficient data to recommend a change from the existing targets and treatment thresholds of a systolic BP target of <130 mmHg and diastolic BP target <80 mmHg.

Role of ACE Inhibitors and ARBs

These guidelines identify specifically those people with diabetes, and those people with evidence of increased urinary albumin excretion, as persons at high risk for CV events. In addition, the recommendations also recognize those people with known CVD, renal disease or elevated urinary albumin excretion, as well as those people with additional CV risk factors to be high-risk people who should receive an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB) as first-line therapy (see Cardiovascular Protection in People with Diabetes chapter, p. S162). This risk-assessment strategy is consistent with long-standing recommendations by both Hypertension Canada and Diabetes Canada that are based on multiple, large scale randomized controlled trials (24,25).

Antihypertensive Choices

Using ACE inhibitors or ARBs as first-line therapeutic agents is appropriate for persons at high risk for CV events. Based on publication of the diabetes subgroup results from the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) (26), dihydropyridine calcium channel blockers (CCBs) were added to the list of potential first-line agents for persons with diabetes and with normal urinary albumin excretion (<30 mg/day). In the ALLHAT study subgroup, 13,101 participants with type 2 diabetes were randomly assigned to chlorthalidone, amlodipine or lisinopril. Although systolic BP was significantly lower among those participants randomly assigned to chlorthalidone compared with lisinopril or amlodipine, no difference was shown in primary endpoint of combined fatal coronary heart disease or non-fatal or fatal MI (HR 0.97, 95% CI 0.86–1.10) between amlodipine and chlorthalidone. While this lack of difference was consistent generally for other CV secondary endpoints, the study was underpowered to detect differences in development of end stage renal disease (ESRD). Thus, the proviso was added that ACE inhibitors and ARBs also appear to have renal benefits beyond that expected from their BP-lowering effects; therefore, health-care providers may wish to consider these additional benefits when selecting first-line agents.

Role of Combination Therapy

If target BP levels are not achieved with standard-dose monotherapy, additional antihypertensive therapy should be used. For persons in whom combination therapy with an ACE inhibitor is being considered, a dihydropyridine CCB is preferable to a thiazide/thiazide-like diuretic. The recommendation supporting ACE/CCB combination therapy in people with type 2 diabetes is based on the Avoiding Cardiovascular events through Combination therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial, which compared benazepril/amlodipine combination treatment vs. benazepril/thiazide therapy (27). The primary endpoint was a composite of MI, stroke, CV death, hospitalization for angina, resuscitated cardiac arrest and coronary revascularization. The trial enrolled 6,946 high-risk participants with type 2 diabetes; 2,842 participants were deemed to be particularly “high risk” by virtue of a previous cardiac, cerebrovascular or renal event. Benazepril/amlodipine reduced occurrence of the primary event compared to benazepril/thiazide in all subjects with diabetes (8.8 vs. 11%; HR 0.79, 95% CI

0.68–0.92) and subgroups of subjects who were considered high risk (13.6 vs. 17.3%, HR 0.77, 95% CI 0.64–0.93).

Single pill combination therapy (SPC) is recommended as an initial treatment option to facilitate the achievement of lower blood pressures, to improve CV outcomes, promote adherence, and reduce medication side effects, relative to using maximal dose monotherapy (28). The improved therapeutic efficiency and efficacy of SPCs were documented in adults in the Heart Outcomes Prevention Evaluation-3 study where one-third had hypertension, 6% had early diabetes and 12% had impaired fasting or impaired glucose tolerance (29). While there is insufficient evidence at this time to make a strong recommendation for the use of SPCs in adults with diabetes, the benefits documented in other hypertensive populations is noteworthy. Historically, the early use of combination therapy was encouraged only in the context of significantly elevated BP (i.e. >20 mmHg above systolic target, or >10 mmHg above diastolic target), but given the evolving evidence for early use of SPCs, the tight linkage of combination therapy to degree of blood pressure elevation warrants re-evaluation.

Harmonization with Hypertension Canada

This chapter was completed in accordance with a memorandum of understanding with Hypertension Canada to produce harmonized guidelines for the management of hypertension in adults with diabetes. The methods used in this chapter were as per the Hypertension Canada Guidelines Committee and have been published previously (30). In brief, annual literature reviews were performed from 2013 to the present by a Cochrane-trained librarian searching for evidence on the management of hypertension in people with diabetes. Each abstract was reviewed by at least 2 people with concordance on the articles put forward for review to update the guidelines. These articles were assessed by a committee of experts whose conflicts of interest are listed with Diabetes Canada and Hypertension Canada, and recommendations passed on to the Central Review Committee. This committee of epidemiological experts, with no conflicts of interest, reviewed the recommendations and presented these at the Hypertension Canada consensus meeting, to stakeholders and, finally, to the Steering Committee of the Diabetes Canada 2018 Clinical Practice Guidelines.

RECOMMENDATIONS

1. People with diabetes mellitus should be treated to attain systolic BP of <130 mmHg [Grade C, Level 3 (11)] and diastolic BP of <80 mmHg [Grade B, Level 1 (7)] (these target BP levels are the same as BP treatment thresholds).

2. For people with CVD or CKD, including albuminuria, or with CV risk factors in addition to diabetes and hypertension, an ACE inhibitor or an ARB is recommended as initial therapy [Grade A, Level 1A (31–34)].

3. For people with diabetes and hypertension not included in other recommendations in this section, appropriate choices include (in alphabetical order): ACE inhibitors [Grade A, Level 1A (26), ARBs [Grade A, Level 1A (29), dihydropyridine CCBs [Grade A, Level 1A (26), and thiazide/thiazide-like diuretics [Grade A, Level 1A (26)].

4. If target BP levels are not achieved with standard-dose monotherapy, additional antihypertensive therapy should be used. For people in whom combination therapy with an ACE inhibitor is being considered, a dihydropyridine CCB is preferable to a thiazide/thiazide-like diuretic [Grade A, Level 1A (26)].

Abbreviations:
ACE, angiotensin converting enzyme; *ARB,* angiotensin receptor blocker; *BP,* blood pressure; *CCB,* calcium channel blocker; *CI,* confidence interval; *CKD,* chronic kidney disease; *CVD,* cardiovascular disease; *HR,* hazard ratio; *MI,* myocardial infarction; *SPC,* single pill combination.

Author Disclosures

Dr. Tobe reports support from AbbVie, Bayer, Servier, Valeant, Pfizer; and personal fees from Heart and Stroke Foundation/ Northern Ontario School of Medicine, outside the submitted work. Dr. Gilbert reports grants and personal fees from AstraZeneca, and Boehringer Ingelheim, personal fees from Janssen, and Merck, outside the submitted work. Dr. Leiter reports grants and personal fees from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, Novo Nordisk, Amgen, and Sanofi; personal fees from Servier and Novartis; grants from GSK, Esperion, Kowa, and The Medicines Company, outside the submitted work. Dr. Prebtani reports support from Servier, outside the submitted work. No other authors have anything to disclose.

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