Hypertension in people with type 2 diabetes

Update on pharmacologic management

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Abstract

Objective To summarize the evidence for the need to improve pharmacologic management of hypertension in people with type 2 diabetes and to provide expert advice on how blood pressure (BP) treatment can be improved in primary care.

Sources of information Studies were obtained by performing a systematic review of the literature on hypertension and diabetes, from which management recommendations were developed, reviewed, and voted on by a group of experts selected by the Canadian Hypertension Education Program and the Canadian Diabetes Association; authors' expert opinions on optimal pharmacologic management were also considered during this process.

Main message The pathogenesis of hypertension in patients with diabetes is complex, involving a range of biological and environmental factors and genetic predisposition; as a result, hypertension in people with diabetes incurs higher associated risks and adverse events. Mortality and morbidity are heightened in diabetes patients who do not achieve BP control (ie, a target value of less than 130/80 mm Hg). Large randomized controlled trials and meta-analyses of randomized controlled trials have shown that reducing BP pharmacologically is single-handedly the most effective way to reduce rates of death and disability in patients with diabetes, particularly associated cardiovascular risks. Often, combinations of 2 or more drugs (diuretics, angiotensin-converting enzyme inhibitors, β-blockers, angiotensin receptor blockers, calcium channel blockers, spironolactone, etc) are required for pharmacotherapy to be effective, particularly for patients in whom BP is difficult to control. However, the health care costs associated with extensively lowering BP are substantially less than the costs associated with treating the complications that can be prevented by lowering BP.

Conclusion Detecting and managing hypertension in people with diabetes is one of the most effective measures to prevent adverse events, and pharmacotherapy is one of the most effective ways to maintain target BP levels in primary care.

KEY POINTS More than 1 million Canadian adults have both diabetes and hypertension, two-thirds of whom have uncontrolled blood pressure (BP); these individuals are at increased risk of cardiovascular events and stroke. More intensive reduction of BP, by at least 6/4 mm Hg, reduces overall premature mortality rates by about 25%; however, 3 or more drugs are often required, and even then many patients do not reach the intended BP target levels. Nonetheless, reducing BP pharmacologically is one of the few medical therapies that decreases overall health care costs and that has been shown to result in large reductions in rates of death and disability. Health care professionals should redouble their efforts to control BP in people with diabetes, and physicians should be comfortable individualizing complex multidrug antihypertensive regimens; resources to assist physicians and patients are available online at **www.htnupdate.ca.**

POINTS DE REPÈRE Au Canada, plus d'un million d'adultes diabétiques sont également hypertendus, et chez les deux tiers d'entre eux, la tension artérielle (TA) est mal contrôlée; ces patients ont un risque accru de problèmes cardiovasculaires et d'accidents vasculaires cérébraux. Une réduction de la TA d'au moins 6/4 mm Hg diminue le taux global de mortalité prématurée d'environ 25%; toutefois, cela requiert souvent 3 médicaments ou plus et même dans ce cas, plusieurs patients n'atteignent pas les niveaux cibles de TA. Néanmoins, une réduction pharmacologique de la TA est une des rares interventions médicales à diminuer les coûts globaux de la santé et à s'être montrées en mesure de produire une importante réduction des taux de mortalité et d'incapacité. Les professionnels de la santé devraient redoubler d'efforts pour contrôler la TA chez les diabétiques, et les médecins devraient être à l'aise avec un traitement individualisé comprenant plusieurs anti-hypertenseurs; le site **www.htnupdate.ca** est susceptible d'aider les médecins et patients.

L'hypertension chez les diabétiques de type 2

Mise à jour sur le traitement pharmacologique

Résumé

Objectif Résumer les données qui rappellent la nécessité d'améliorer le traitement pharmacologique de l'hypertension chez

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les diabétiques de type 2 et de fournir des conseils d'experts sur la façon d'améliorer le traitement de la tension artérielle (TA) en contexte de soins primaires.

Source de l'information À partir d'études recueillies grâce à une revue systématique de la littérature sur l'hypertension et le diabète, on a élaboré et révisé des recommandations et on les a soumises au vote d'un groupe d'experts du Programme éducatif canadien sur l'hypertension et de l'Association canadienne du diabète; on a également tenu compte de l'opinion avisée des auteurs sur le traitement pharmacologique optimal.

Principal message La pathogénie de l'hypertension chez les diabétique est complexe et fait intervenir plusieurs facteurs biologiques et environnementaux ainsi qu'une prédisposition génétique; par conséquent, l'hypertension du diabétique présente un plus grand danger de problèmes et de complications. Les diabétiques qui n'obtiennent pas un contrôle de la TA (c'est-à-dire une valeur cible de moins de 139/80 mm Hg) ont un taux de mortalité et de morbidité plus élevé. De vastes essais cliniques randomisés et des méta-analyses d'essais cliniques randomisés ont montré qu'à elle seule, une réduction pharmacologique de la TA est la façon la plus efficace de réduire les taux de décès et d'incapacité chez le diabétique, notamment le risque de problèmes cardiovasculaires. Pour que le traitement soit efficace, il est souvent nécessaire d'utiliser deux médicaments ou plus (diurétiques, inhibiteurs de l'enzyme de conversion de l'angiotensine, bloqueurs β, bloqueurs des récepteurs de l'angiotensine, bloqueurs des canaux calciques, spironolactone, etc.), en particulier chez les patients dont la TA est difficile à contrôler. Toutefois, les coûts de santé engendrés par une réduction importante de la TA sont considérablement moindres que ceux associés au traitement des complications qui peuvent être prévenues par l'abaissement de la TA.

Conclusion La détection et le traitement de l'hypertension chez le diabétique sont parmi les mesures les plus efficaces pour prévenir les complications tandis que la pharmacothérapie est une des façons les plus efficaces pour maintenir des niveaux cibles de TA en contexte de soins primaires.

Increased blood pressure (BP) is a leading risk factor for death and disability, particularly in people with diabetes. Over the past few years, the incidence of hypertension and diabetes in Canadian adults has increased substantially.[1] Close to 6 million adult Canadians were diagnosed with hypertension in 2007 (a 52% increase from 1997 to 1998) and about 2 million Canadians were diagnosed with type 2 diabetes from 2006 to 2007 (a 25% increase from 2002 to 2003).[1,2] Between 2007 and 2008, more than 1 million Canadians had a diagnosis of both hypertension and diabetes, representing 1 in 4 Canadians with hypertension and two-thirds of those with diabetes.[1] The mortality rates for Canadians with diagnosed hypertension and diabetes are 2.5 times higher than those of Canadians without either condition.[1] The clinical characteristics of diabetes and hypertension in diabetes patients can be found in **Table 1**.[3]

Table 1. Clinical description of diabetes and hypertension in the presence of diabetes

CONDITION	CLINICAL CHARACTERISTICS
Diabetes	Fasting plasma glucose level of > 7 mmol/L; casual plasma glucose level of > 11.1 mmol/L, with symptoms of diabetes; or 2-hour plasma glucose level of > 11.1 mmol/L
Hypertension in people with diabetes	Systolic BP value of > 130 mm Hg or diastolic BP value of > 80 mm Hg

BP—blood pressure.
Data from the Canadian Diabetes Association Clinical Practice Guidelines Expert Committee.[3]

Most (60% to 80%) people with type 2 diabetes die of cardiovascular complications, and up to 75% of specific cardiovascular complications have been attributed to high BP (**Table 2**).[4,5] Hypertension is also a primary contributing factor to kidney failure and eye disease in people with diabetes.[6,7] A recent Ontario survey demonstrated a marked improvement in BP control in hypertensive people with and without diabetes[8,9]; the improved treatment of hypertension in Canada has been associated with a marked reduction in death and hospitalization from cardiovascular disease.[10,11] Still, approximately two-thirds of people with diabetes do not reach recommended target BP values (ie, less than 130/80 mm Hg),a much higher proportion than patients without diabetes.[9]

Table 2. Proportion of diabetic complications attributable to hypertension*

COMPLICATION	ATTRIBUTABLE RISK, %
Stroke	75
Coronary artery disease	35
End-stage renal disease	50
Eye disease†	35
Leg amputation	35

BP—blood pressure.
Data from Bild and Teutsch.[4]
*Hypertension has been defined as BP > 160/95 mm Hg or BP > 140/90 mm Hg, depending on the study.[4,5]
†Retinopathy.

In 2009, the College of Family Physicians of Canada endorsed a call to action to improve BP control in people with diabetes. Clearly this is a high-priority area of improvement, one that will result in large reductions in death and disability rates and health care costs. This article will summarize the evidence for the need to improve the pharmacologic management of hypertension in people with type 2 diabetes and will provide expert advice on how BP treatment can be improved.

Quality of evidence

The evidence used in this review is derived from the hypertension management recommendations process of the Canadian Hypertension Education Program (CHEP). Since 1999 the program has annually reviewed hypertension and related literature, and has continued to evolve with increases in membership and activities.[12,13] A subgroup of experts (7 members in 2009) jointly selected by the Canadian Diabetes Association and the CHEP Executive Committee selects studies on the basis of a literature search conducted by a Cochrane librarian and develops draft recommendations using an evidence-based grading and classification system. A summary of the literature with references and draft recommendations is then reviewed by the Central Review Committee (7 members in 2009).[14] Members of the Central Review Committee are trained methodologists without financial conflicts of interest. The Central Review Committee and the subgroup of experts negotiate differences of opinion in interpretation of the literature and potential recommendations. A member of the Central Review Committee presents the literature and recommendations to the CHEP Recommendations Task Force (56 members in 2009), and a consensus on the potential recommendations is developed. Potential recommendations are subsequently presented at an open national meeting and are voted on by the Recommendations Task Force; recommendations that receive less than 70% support are removed. A series of steps has been incorporated into the process to reduce the influence of financial conflicts of interest, which is a priority.[13]

There is a strong history of basing pharmacologic recommendations only on evidence of improved patient outcomes from randomized controlled trials or meta-analyses of randomized controlled trials. However, the diabetes recommendations presented in this summary include specific advice on how to combine drugs based both on the authors' expert opinions and general concepts from CHEP publications that concern combining treatments.

Main findings

Mechanisms of higher risk from increased BP in people with diabetes. The pathogenesis of hypertension in diabetes is complex, involving strong interactions between genetic predisposition and a range of environmental and biological factors such as unhealthy eating, sedentary behaviour, sodium retention, abdominal obesity, autonomic derangements, premature arterial stiffening, and endothelial dysfunction. Not only are patients with diabetes more likely to have coexistent hypertension, but any given systolic BP value in patients with diabetes is associated with a more than 2-fold increase in age-adjusted cardiovascular death rates.[15] For example, a diabetic patient with a systolic BP between 120 and 139 mm Hg has a similar cardiovascular mortality rate to a patient without diabetes whose systolic BP is 160 to 179 mm Hg. The exact cause of the increased morbidity and mortality associated with hypertension in people with diabetes independent of other risk factors is unclear. However, the frequent absence of the usual nocturnal BP dip among patients with diabetes is likely to be contributory. Despite similar daytime office and home BP recordings, a "non-dipper" will have higher 24-hour and nocturnal BP values, with the latter in particular being a strong predictor of cardiovascular death.[16]

Selected evidence supporting reducing BP with pharmacotherapy in people with type 2 diabetes. Pharmacologically reducing BP in people with diabetes is one of the most effective medical interventions available to prevent death and disability. Randomized controlled trials of BP-lowering treatments in people with diabetes have demonstrated substantial reductions in death, cardiovascular disease, eye disease, and kidney disease rates, and the benefits are accrued in a short time.[6,7,17-21] For example, in the Syst-Eur (Systolic Hypertension in Europe) trial, in which isolated systolic hypertension was clinically defined as having a systolic BP value of more than 160 mm Hg and a diastolic BP value of less than 90 mm Hg, active treatment reduced cardiovascular mortality by 76% (number needed to treat [NNT] was approximately 21 for 2 years' treatment) and all cardiovascular events by 67% (NNT approximately 13 for 2 years' treatment), with a reduction in BP of 9.8/3.8 mm Hg.[22] In the diabetes subgroup of the HOT (Hypertension Optimum Treatment) trial, those who were assigned to a target diastolic BP of less than 80 mm Hg were compared with those assigned to a target BP of less than 90 mm Hg. Although the achieved difference in BP values between the 2 groups at the end of the study was only 4 mm Hg, this greater reduction in BP levels still resulted in a 66% risk reduction of death from heart disease and stroke (NNT approximately 36 for 3.8 years' treatment).[23] In a meta-analysis of randomized controlled trials of people with diabetes and hypertension, more versus less intensive lowering of BP reduced BP values by an additional 6/4 mm Hg and reduced total mortality by 27% (95% confidence interval

5% to 44%) and major cardiovascular events by 25% (95% confidence interval 6% to 39%).[24] The use of an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB) therapeutic regimen to lower BP has additional advantages in people with chronic kidney disease and microalbuminuria or macroalbuminuria.[24]

The patients with diabetes in the aforementioned clinical trials often had additional cardiovascular risks that were not treated as intensively as is currently recommended in clinical practice. It was hypothesized that these features would increase the absolute (but not the relative) benefits of the antihypertension treatment, resulting in a lower NNT than might normally occur. In particular, larger numbers of people with diabetes at lower cardiovascular risk (recently diagnosed or younger people, those without additional cardiovascular risks, and those with lower baseline BP values) would be expected to require treatment to prevent the events calculated from the indicated clinical trials. Nevertheless, the benefits of antihypertension treatment have been documented in recent trials and even in a clinical trial that included people with baseline BP levels below 130/80 mm Hg.[20] Further, many Canadians with diabetes still do not receive adequate treatment for other established cardiovascular risks, such as dyslipidemia.[25]

Very recently, the results of the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial, which randomized people with diabetes to a target systolic BP value of either less than 140 mm Hg or less than 120 mm Hg, were published.[26,27] The primary outcome (a composite of myocardial infarction, stroke, and cardiovascular death) was not significantly different between the interventions. Stroke was reduced (0.21% absolute fewer strokes per year, relative risk reduction 41%), but serious adverse events were higher (absolute increase from 1.3% to 3.3%, largely owing to hypotension, syncope, bradycardia, and hyperkalemia during the 5-year trial) in the group targeted to the systolic BP value of less than 120 mm Hg. The effect of the ACCORD trial on target BP recommendations in people with diabetes has yet to be considered by the CHEP and the Canadian Diabetes Association, but notably the ACCORD trial did not assess the influence of antihypertensive management on the current recommended BP target value of less than 130/80 mm Hg. Updated recommendations and reviews of the evidence can be found at **www.hypertension.ca**.

Initial pharmacotherapy based on CHEP recommendations. An ACE inhibitor or an ARB is a potential first-line therapy in all people with hypertension and diabetes.[14] Alternative first-line treatments include long-acting calcium channel blockers (CCBs) and low-dose diuretics in people without microalbuminuria.[14] Diuretic therapy reduces major cardiovascular events in hypertensive people with or at risk for diabetes to an extent similar to that of long-acting CCBs or ACE inhibitors.[28] A combination of 2 medications should be considered for initial therapy if BP is 150/90 mm Hg or higher.

Expert advice on combination pharmacotherapy to control hypertension. A survey in Ontario revealed that 27% of patients with diabetes who had uncontrolled BP were not treated and only 45% of those taking multiple drugs were prescribed a diuretic.[8] Current data suggest that failure to intensify pharmacotherapy is the primary reason for lack of BP control. In clinical trials, combinations of 4 or more drugs are sometimes required for BP control.[29] Physicians caring for people with hypertension and diabetes need to be comfortable individualizing complex antihypertensive regimens according to their patients' clinical profiles.

Combinations of 2 drugs. In general, the drugs prescribed in combination should be selected from initial therapy options. A notable exception is the combination of an ACE inhibitor with an ARB, which has more adverse effects than ACE inhibitor therapy alone and has no therapeutic advantage over either drug alone.[30,31] As such, ACE inhibitor and ARB combination therapy is specifically not recommended unless there is macroalbuminuria or resistant heart failure, for which the combination might have additional advantages. Studies show that people with hypertension at high cardiovascular risk owing to diabetes or other diseases have a greater risk reduction for cardiovascular events when treatment is with an ACE inhibitor plus a CCB rather than an ACE inhibitor plus a diuretic[32]; physicians should consider this combination in high-risk patients.[14]

Combinations of 3 and 4 drugs. In the absence of contraindications, diuretics are generally advised for patients in whom BP is difficult to control[33]; often, higher doses of diuretic medications are required in resistant hypertension.[34] Maintaining a normal serum potassium level is important to minimize the effect of diuretics on blood glucose levels and to maximize cardiovascular event reductions.[35,36] Potent 3-tablet (4-drug) BP-lowering combinations usually comprise a tablet containing a diuretic and either an ACE inhibitor or an ARB, plus 2 of the following: a tablet containing a long-acting CCB; a tablet containing spironolactone; or a tablet containing a long-acting β-blocker. Regular monitoring of serum potassium is recommended if spironolactone is prescribed, especially if baseline serum potassium levels are in the high end of the normal range, if glomerular filtration rate is reduced, or if there is concurrent use of other drugs that cause potassium reduction.

Although multiple drugs are required for BP control, extensive lowering of BP in people with diabetes is one

of the very few cost–saving medical interventions (ie, the cost of BP lowering is less than the cost of the complications prevented by BP lowering).[37] Furthermore, quality of life can improve with more intensive BP lowering.[38] Referral to another specialist or primary care physician with expertise in lowering BP should be considered if BP cannot be controlled.

People with diabetes and hypertension usually have other cardiovascular risks. Although hypertension is a leading risk factor in people with diabetes, other health risks are also very important. Experts recommend that people with hypertension and diabetes be assessed and appropriately managed for dyslipidemia, smoking, elevated blood glucose levels, abdominal obesity, sedentary behaviour, and unhealthy eating habits. Lifestyle changes and medication adherence remain the cornerstone to attaining and maintaining target BP values. Current evidence is unclear as to the role of acetylsalicylic acid (ASA) in people with diabetes and hypertension. In the HOT trial, hypertensive people benefited from ASA therapy, with reduced cardiovascular events.[23] However, there is a lack of benefit of ASA therapy in the primary prevention of cardiovascular disease in studies of people with diabetes.[39-41] Finally, a comprehensive program that includes lifestyle changes and pharmacotherapy for multiple risk factors has been associated with a more than 40% reduction in total mortality over 8 years (NNT of 5 to prevent death), highlighting the importance of integrated programs that assess and address all cardiovascular risks.[42]

Conclusion

Detecting and managing hypertension in patients with diabetes is one of the most effective things that can be done to prevent adverse events. All health care professionals must redouble their efforts to improve the rates of hypertension control in patients with diabetes. The effects of improving BP control on mortality and cardiovascular event rates are substantial and result in cost savings for the health care system. To assist physicians, nurses, pharmacists, and other health care professionals in tackling the problem of inconsistent hypertension management in patients with diabetes, Hypertension Canada, the Heart and Stroke Foundation of Canada, and the Canadian Diabetes Association are developing knowledge translation programs aimed at health care professionals and people with diabetes. Health care professionals can be automatically notified of updated or new resources via e-mail by signing up at **www.htnupdate.ca** and people with diabetes can receive updates by signing up at **www.myBPsite.ca.** Updated recommendations and reviews of the evidence can be found at **www.hypertension.ca.**

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Competing interests

Dr Gilbert has served on advisory boards, received research grant funding, and given lectures for AstraZeneca, Bristol-Myers Squibb, and Novartis. **Dr Leiter** has received research funding from, has provided continuing medical education on behalf of, or has acted as a consultant to Abbott Laboratories, AstraZeneca, Boehringer Ingelheim, Eli Lilly, GlaxoSmithKline, Merck, Novartis, Novo Nordisk, Roche, Sanofi-Aventis, and Servier. **Dr Larochelle** has received support for continuing education and research grants from Pfizer, Merck, Boehringer Ingelheim, Servier, and AstraZeneca. **Dr Tobe** has received research grants and speaker's honoraria from Abbott Laboratories, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Janssen, Merck, Novartis, Pfizer, Sanofi-Aventis, and Servier. **Dr Ward** has received funding from AstraZeneca, Boehringer Ingelheim, Merck, Novo Nordisk, Sanofi-Aventis, and Pfizer. None of the other authors has any competing interests to declare.

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