Uncertainty about the systolic blood pressure target in people with diabetes

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The article by Campbell et al[1] on hypertension in people with type 2 diabetes, which appeared in the September 2011 issue of *Canadian Family Physician*, provides a succinct overview of the topic and important information for family physicians. Our aim is to complement the article by expanding on some management areas where there is uncertainty, specifically the definition of hypertension and the current recommended target blood pressure (BP) of less than 130/80 mm Hg. While the article by Campbell et al refers to both systolic BP (SBP) and diastolic BP (DBP), most of our comments will address the former, as SBP is considered more important for determining the risk of cardiovascular events.[2,3]

Hypertension in people with diabetes is defined as the presence of SBP greater than 130 mm Hg or DBP greater than 80 mm Hg,[1] the implication being that people with diabetes who have BPs greater than these values should receive treatment. Indeed, the current Canadian hypertension guideline recommends that treatment be initiated at a BP of 130/80 mm Hg or greater.[4] However, family physicians might not know that in the most recent Canadian Diabetes Association (CDA) guideline this is a grade D, or *consensus*, recommendation.[5] Indeed, no study has compared the effects of starting therapy in patients with diabetes with SBPs of 130 to 139 mm Hg compared with patients with SBPs of 140 mm Hg or greater, the recommended level for starting therapy in people without diabetes.[6] Thus, as indicated by the grade D rating of the CDA recommendation, there is considerable uncertainty about the SBP at which to initiate treatment.

This uncertainty extends to the SBP treatment target of less than 130 mm Hg. While there is no doubt that lowering SBP lowers cardiovascular risk in people with diabetes, the level to which it should be lowered is uncertain. Campbell et al correctly point out several studies that have shown benefit with antihypertensive therapy in decreasing microvascular and macrovascular outcomes.[7-13] However, mean SBP in the active therapy group was lowered to less than 130 mm Hg in only one study: the ABCD NT (Appropriate Blood Pressure Control in Diabetes—Normotensive) trial.[11] In 4 studies,[7,8,12,13] subjects were not randomized to different BP targets but to different drug regimens versus placebo, and it is not possible to definitively determine if the observed benefit was derived from reaching specific SBP targets or from the drugs. In 2 studies,[7,8] benefits in renal outcomes were independent of mean BPs.

Results of ABCD NT

The ABCD NT trial is the only randomized controlled trial (RCT) cited by the CDA guideline to support a target SBP of less than 130 mm Hg.[5] This small study randomized 480 patients with type 2 diabetes to different DBP targets. The intensive therapy group received nisoldipine or enalapril to achieve a DBP reduction of 10 mm Hg from the baseline measurement. The moderate therapy group received placebo and aimed for a DBP of 80 to 89 mm Hg. After a mean of 5.3 years, the achieved BPs were 128/75 mm Hg and 137/81 mm Hg in the intensive and moderate therapy groups, respectively. There was no statistically significant difference in the primary outcome of change in creatinine clearance. However, there was benefit in some secondary outcomes including stroke, proteinuria, and retinopathy.

The CDA acknowledges the limitations of ABCD NT and gives the recommendation to achieve an SBP of less than 130 mm Hg a grade C evidence level, indicating it is based on a non-randomized clinical trial or cohort study. The CDA also cites 2 cohort studies supporting an SBP target of less than 130 mm Hg.[14,15] However, while these 2 observational studies indicate fewer microvascular and macrovascular outcomes with lower SBP, they do not prove that lowering SBP with antihypertensive medication will lead to fewer such outcomes and do not provide definitive evidence for a specific treatment target. Again, family physicians might not be aware of the low quality of evidence supporting the recommended SBP target of less than 130 mm Hg.

Results of ACCORD BP

The publicly funded ACCORD BP (Action to Control Cardiovascular Risk in Diabetes—Blood Pressure) trial was designed to address this lack of RCT evidence[16] and, according to the CDA guidelines, would provide stronger evidence for an optimal SBP treatment target.[5] The ACCORD BP trial was a large study (N = 4733) that randomized patients with type 2 diabetes to a target SBP of less than 120 mm Hg or less

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than 140 mm Hg.[16] Mean baseline BP was 139/76 mm Hg. Both groups were allowed to take the same medications. After a mean of 4.7 years, mean BPs were 119/64 mm Hg and 134/71 mm Hg in the intensive and moderate treatment groups, respectively. There was no significant difference between the 2 groups in the primary composite outcome of myocardial infarction (MI), stroke, and death. There was a statistically significant reduction in the risk of stroke (2.6% vs 1.5%, absolute risk reduction 1.1%, number needed to treat 92 [95% CI 53 to 356]). However, there was also an increase in serious adverse events with a number needed to harm of 50 (95% CI 35 to 87) (**Table 1**).[16,17] While ACCORD BP did not test an SBP target of less than 140 mm Hg against a target of less than 130 mm Hg, it is unlikely that a target of 130 mm Hg would be preferable, as even a target of 120 mm Hg did not provide benefit.[16] An SBP target of less than 120 mm Hg might lead to a small reduction in stroke, and some patients might wish to incur the extra costs and possible adverse effects of intensive BP lowering if they place a high value on stroke prevention.[18]

Evidence for identifying an SBP target

The RCT evidence for and against an SBP target of less than 130 mm Hg revolves around 2 studies, ABCD NT[11] and ACCORD BP.[16] The CDA and the Canadian Hypertension Education Program have not changed their recommendations since ACCORD BP was published and presumably are basing their recommendations on ABCD NT. **Table 2**[4,5,11,16] summarizes the key features of the 2 RCTs.

Uncertainty about efficacy is not the only factor to consider when identifying an appropriate SBP target. It is also important to consider the safety and practicality of reaching the target. Osher et al aimed to reduce BP in 257 patients with type 2 diabetes to less than 130/85 mm Hg, as was recommended when the study was conducted.[19] Initial mean BP was 159/86 mm Hg, reflecting that most patients were already taking antihypertensive medications. An SBP of 130 mm Hg was reached by only 33% of patients, and DBP was lowered to 70 mm Hg or lower in 57% of patients. Lower DBPs were associated with advancing age, higher initial SBPs, and pre-existing coronary artery disease. The decline in DBP was not associated with any drug class or combination of drugs. The authors concluded that attempted lowering of SBP to less than 130 mm Hg is associated with inordinate lowering of DBP in a substantial number of patients. They also questioned if the benefits of tight SBP control to less than 130 mm Hg outweighed the risks of excessive diastolic reduction, especially in older patients with diabetes or those with coronary artery disease and diabetes.

The question of harm from excessive lowering of DBP remains unanswered. A recent meta-analysis of 31 BP-lowering trials in 73 913 persons with diabetes found no evidence of increased risk of MI from excessive lowering of DBP.[20] However, this finding was not based on individual patient data but on meta-regression, which is like an epidemiologic study of the included RCTs. Therefore, results might have been affected by unknown confounding variables.[18,21]

A secondary analysis of INVEST (International Verapamil-Trandolapril Study) did find evidence of harm. The original INVEST trial randomized 22 576 patients with hypertension and coronary artery disease

Table 1. Results of the ACCORD BP trial[16]: *A) Efficacy outcomes and B) adverse events.*

A) EFFICACY OUTCOMES	SBP TARGET, % < 140 mm Hg (MODERATE)	SBP TARGET, % < 120 mm Hg (INTENSIVE)	ARR, %	RRR, %	NNT (95% CI) FOR 4.7 Y*
Primary outcome (nonfatal MI, nonfatal stroke, death from cardiovascular causes)	10.0	8.8	1.2	11.9	NS
Stroke	2.6	1.5	1.1	41.7	92 (53-356)
Macroalbuminuria	8.7	6.6	2.1	24.5	47 (27-179)
B) ADVERSE EVENTS	**SBP TARGET, % < 140 mm Hg (MODERATE)**	**SBP TARGET, % < 120 mm Hg (INTENSIVE)**	**ARI, %**	**RRI, %**	**NNH (95% CI) FOR 4.7 Y**
Total mortality	6.1	6.3	0.2	4.5	NS
Serious adverse events from antihypertensive medication†	1.3	3.3	2.0	157.5	50 (35-87)
Potassium level < 3.2 mmol/L	1.1	2.1	1.0	82.1	107 (61-457)
eGFR < 30 mL/min/1.73 m^2	2.2	4.2	0.9	91.1	50 (33-100)

ARI—absolute risk increase, ARR—absolute risk reduction, eGFR—estimated glomerular filtration rate, MI—myocardial infarction, NNH—number needed to harm, NNT—number needed to treat, NS—not statistically significant, RRI—relative risk increase, RRR—relative risk reduction, SBP—systolic blood pressure.

*NNT and 95% CI calculated with the Dalhousie University Katie Clinical Significance Calculator.[17]

†Serious adverse events are those that are life-threatening, cause permanent disability, or require hospitalization.

Table 2. Summary of the ACCORD BP[16] and ABCD NT[11] trials

PARAMETER	ACCORD BP	ABCD NT
Objective	Test effect of target SBP < 120 mm Hg on major cardiovascular events among high-risk persons	Determine the effect of moderate vs intensive DBP control on change in creatinine clearance
N	4733	480
Duration	4.7 y	5.3 y
Population	People with type 2 diabetes	People with type 2 diabetes
Prevalence of cardiovascular disease	34%	24% in intensive group 31% in control group
Age, y		
• Inclusion	Inclusion criteria of ≥ 40 with cardiovascular disease and ≥55 with at least 2 risk factors	Patients were between the ages of 40 and 74 at the time of recruitment
• Mean age at baseline	62	59
Drugs	Both groups able to take diuretic, β-blocker, ACE, ARB, CCB	Nisoldipine or enalapril vs placebo
Inclusion SBP	130-170 mm Hg if taking 0-3 antihypertensive drugs	NA
Inclusion DBP	NA	80-89 mm Hg while taking no medications
Target SBP	Intensive: < 120 mm Hg Moderate: < 140 mm Hg	NA
Target DBP	NA	Intensive: 10 mm Hg lower than on entry Moderate: 80-89 mm Hg
Mean baseline BP	139/76 mm Hg	136/84 mm Hg
Mean achieved SBP	Intensive: 119 mm Hg Moderate: 134 mm Hg	Intensive: 128 mm Hg Moderate: 137 mm Hg
Mean achieved DBP	Intensive: 64 mm Hg Moderate: 71 mm Hg	Intensive: 75 mm Hg Moderate: 81 mm Hg
Primary outcome	Composite of MI, stroke, and cardiovascular death	Change in 24-h creatinine clearance
Results	No difference in primary outcome No difference in most secondary outcomes with the exception of stroke	No difference in primary outcome Benefit in stroke, proteinuria, retinopathy
Comments from Canadian guidelines	We are not aware of comments from CDA[5]; however, CHEP[4] has not changed recommendations based on ACCORD BP	CDA cites ABCD NT to support SBP target of < 130 mm Hg (grade C recommendation) while acknowledging its limitations (no statistical correction for multiple comparisons, results for some outcomes based on small numbers)

ACE—angiotensin-converting enzyme inhibitor, ARB—angiotensin receptor blocker, BP—blood pressure, CCB—calcium channel blocker, CDA—Canadian Diabetes Association, CHEP—Canadian Hypertension Education Program, DBP—diastolic blood pressure, MI—myocardial infarction, NA—not applicable, SBP—systolic blood pressure.

to antihypertensive therapy based on either a calcium channel blocker or a β-blocker.[22] After a mean of 2.7 years, there was no significant difference in the primary composite outcome of all-cause death, nonfatal MI, and nonfatal stroke between the 2 treatment groups. The secondary analysis explored the relationship between achieved SBP and DBP and the primary outcome and its individual components.[23] The primary outcome, total MI, and total stroke occurred more frequently with a DBP lower than 70 mm Hg than with a DBP of 70 to 90 mm Hg (**Table 3**).[17,23] Although the analysis was based on patient-level data, it has limitations, as it was a post hoc observational study of an RCT and included only 6400 patients with diabetes. Nevertheless, physicians should be aware of the possibility of harm from excessive lowering of DBP when trying to achieve a target SBP of 130 mm Hg or less.

Summary

Patients with diabetes benefit from antihypertensive treatment. The uncertainty is in the recommended target of 130 mm Hg or lower. Achieving such a target can be difficult and there is the possibility of harm. The 2013 American Diabetes Association has updated its target SBP position statement. It states there is level B evidence from well-conducted cohort studies that "People with diabetes and hypertension should be treated to a systolic blood pressure goal of < 140 mm Hg."[24] It also states there is level C evidence from poorly controlled or uncontrolled studies that "Lower systolic targets, such as

Table 3. Association between achieved DBP and outcomes in INVEST reanalysis

EFFICACY OUTCOMES	ACHIEVED DBP, %		ARI, %	RR, %	NNH (95% CI) FOR 2.7 Y
	< 70 mm Hg	70–90 mm Hg			
All-cause death, nonfatal MI, nonfatal stroke	18.4	8.6	9.9	2.1	10 (9-12)
Fatal and nonfatal MI	6.5	3.4	3.1	1.9	32 (24-48)
Fatal and nonfatal stroke	2.2	1.4	0.8	1.6	126 (71-542)

Results calculated from data in Messerli et al[23]; NNH calculated using the Dalhousie University Katie Clinical Significance Calculator.[17]
ARI—absolute risk reduction, DBP—diastolic blood pressure, MI—myocardial infarction, NNH—number needed to harm, RR—relative risk.

< 130 mm Hg, may be appropriate for certain individuals, such as younger patients, if it can be achieved without undue treatment burden."[24]

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Competing interests

None declared

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