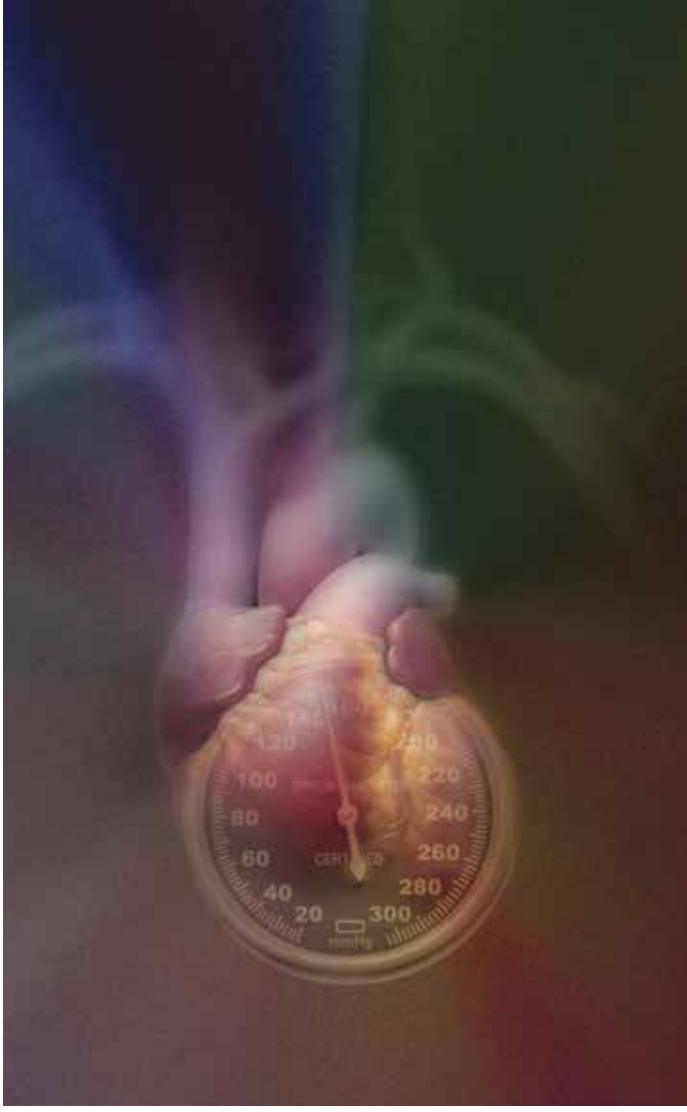
Modern trends in managing hypertension in people with diabetes



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The major cause of mortality in diabetes remains cardiovascular disease (CVD). Thus, any risk factors associated with CVD must be aggressively treated in patients with diabetes. Hypertension is one of these risk factors and should be appropriately managed in such individuals.

Epidemiology of hypertension in diabetes mellitus

The prevalence of hypertension in the population with diabetes is much higher than that seen in the general population both before and after the clinical onset of diabetes.[1] In both international and national surveys of patients with diabetes, such as the Developing Education on Microalbuminuria for Awareness of Renal and Cardiovascular Risk in Diabetes (DEMAND) and the National Evaluation of the Frequency of Renal Impairment Co-existing with Non-insulin-Dependent Diabetes (NEFRON) surveys,[2,3] at least 75% of the patients diagnosed with diabetes had concomitant hypertension.

In type 2 diabetes, hypertension appears to be a feature of the insulin resistance syndrome and can often precede the diagnosis of diabetes. By contrast, in type 1 diabetes, hypertension often is not seen until there is evidence of renal disease. However, in the large Finish Diabetic Nephropathy (FinnDiane) cohort of subjects with type 1 diabetes, ambulatory BP monitoring (ABPM) identified early rises in blood pressure (BP) even before early renal disease was evident.[4]

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Key points

- **The prevalence of hypertension in the population with diabetes is much higher than in the general population.**
- **The significant benefits of lowering blood pressure (BP) in patients with diabetes have been confirmed in recent meta-analyses.**
- **White coat hypertension and loss of diurnal variation are common in subjects with diabetes, so ambulatory BP monitoring is increasingly being used to measure and monitor BP in this population.**
- **Management of hypertension in subjects with diabetes should be individualised, and the benefits and side effects of treatment considered when making decisions about target BP and choice of BP lowering medication.**
- **Current guidelines have become less stringent in terms of initiation of BP lowering medications.**
- **The advent of new glucose lowering drugs such as sodium-glucose cotransporter 2 inhibitors may provide clinicians with additional opportunity to reduce BP.**

Why lower blood pressure?

Diabetes mellitus and hypertension are two closely related conditions, both of which are leading causes of the burden of CVD. The effect of lowering BP in patients with diabetes has been examined in many large, prospective, randomised clinical trials, with recent meta-analyses confirming significant benefits. For example, the UK Prospective Diabetes Study (UKPDS) showed that with improved control of BP in patients with type 2 diabetes, a significant risk reduction in both macrovascular and microvascular diabetic complications can be achieved.[5,6] However, overinterpretation of these findings from almost 20 years ago should be avoided since the level of BP achieved in that trial was much higher than is targeted now in clinical practice.

A recent meta-analysis by Emdin and colleagues showed that a 10 mmHg reduction in systolic BP (SBP) is associated with a lower risk of all-cause mortality, CVD events, coronary heart disease (CHD) events and stroke in subjects with diabetes.[7] The same meta-analysis reported that this 10 mmHg reduction in BP also lowers the risk of microvascular complications such as albuminuria.[7]

As seen in individuals without diabetes, elevated BP is also closely associated with nonfatal and fatal stroke in those with diabetes.[8,9] In the large multinational Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE), a reduction in CV events was observed with BP lowering.[10] In the BP arm of the Action to Control Cardiovascular Risk in Diabetes (ACCORD-BP) study, although aggressive BP lowering achieving an average SBP of about 120 mmHg did not decrease mortality, there was a significant reduction in stroke.[11] In summary, recent randomised controlled trials have clearly confirmed previous benefits of BP lowering on a range of CV endpoints, including myocardial infarction (MI) and stroke.

The benefits of BP lowering in patients with diabetes has led to the suggestion that subjects with diabetes who are normotensive should also be considered for antihypertensive treatment. However, data in such subjects have not been as convincing. Early introduction of angiotensin-converting enzyme (ACE) inhibitors or angiotensin-II receptor blockers (ARBs) in such individuals with either type 1 or type 2 diabetes was not found to be associated with reduced renal disease.[12,13] Interestingly, the one benefit that may occur with early renin–angiotensin system (RAS) blockade in subjects with diabetes is a reduction in retinopathy.[13-15]

Assessing blood pressure

The assessment of BP in individuals with diabetes needs to include evaluation of concomitant CV risk factors such as dyslipidaemia and the presence or absence of renal disease, as assessed by measurement of renal function (e.g. serum creatinine level) and albuminuria. Reliable BP measurements must also be obtained. At each clinic visit, patients' BP should be measured after they have been sitting and rested for at least 5 minutes and with use of an appropriate cuff size, particularly for those who are obese (Box 1).

BP measurements in the office, however, often do not reflect the 'true' BP of the patient, due to the possibility of a 'white coat effect' or 'masked hypertension'.[16] It is also important to assess the nocturnal BP, since diurnal variation of the patient's BP may be lost. This phenomenon, often observed in patients with diabetes and called 'nondipping', has been shown to be strongly associated with target organ damage and CVD risk.[17,18] Because white coat hypertension and nondipping are common in subjects with diabetes, ABPM is increasingly being used in this population (Box 2). Other options for measuring BP include home BP monitoring, although the superiority of this approach over ABPM has not been proven.

1. Clinical approach to blood pressure management

- Take a full history and perform a full clinical examination
- Measure BP after patient has rested for 5 to 10 minutes
- Use appropriately sized BP cuff for patient
- Check for comorbidities (e.g. kidney disease, sleep apnoea, heart failure)
- Confirm if BP is elevated by either ABPM or home BP monitoring
- Consider lifestyle measures (e.g. weight loss, perhaps salt restriction)
- Consider prescribing medications (see Box 3)

Abbreviations: BP = blood pressure; ABPM = ambulatory blood pressure monitoring.

2. Reasons for inadequate blood pressure control in type 2 diabetes

- Noncompliance with medications and/or lifestyle measures
- 'White coat' effect (consider using ABPM to measure BP)
- Secondary causes of hypertension (particularly renal artery stenosis)

Abbreviations: BP = blood pressure; ABPM = ambulatory blood pressure monitoring.

How high is too high?

Controversies on target levels

The issue of what should be the SBP and diastolic BP (DBP) targets in subjects with diabetes remains controversial. Indeed, many recent guidelines have considered less aggressive BP target levels in such subjects. For example, the recent 8th Joint National Committee (JNC 8) guidelines have revised the level for the initiation of BP lowering treatment from 130 mmHg to 140 mmHg for SBP and from 80 mmHg to 90 mmHg for DBP in adults with diabetes.[19] The reason for this decision was primarily based on the ACCORD-BP trial, which showed that targeting a SBP of less than 120 mmHg, compared with less than 140 mmHg, did not lead to a statistically significant reduction in the outcome of CV death, nonfatal MI and nonfatal stroke in patients with type 2 diabetes and hypertension.[11] Indeed, the JNC 8 report stated that since there is insufficient evidence to support a target BP level of 130/80 mmHg, the target in diabetes should be 140/90 mmHg, as is recommended in the general population.

The American Diabetes Association (ADA) also recommends a target BP level of less than 140/90 mmHg in people with diabetes, yet points out that lower target levels such as less than 130/80 mmHg

3. Selecting antihypertensive agents in diabetes mellitus

- Use any of the major classes as first-line therapy (some authorities would avoid diuretics first line)
- If patient has renal disease: an ACE inhibitor or ARB should be used first line
- Avoid dual ACE inhibitor/ARB use
- Consider CCB as a second-line agent
- Consider comorbidities when selecting medications:
  - if patient has heart failure: consider diuretics, avoid alpha-blockers
  - if patient has peripheral vascular disease: avoid beta-blockers
  - if patient has angina: consider CCBs such as verapamil

Abbreviation: ACE = angiotensin converting enzyme; ARBs = angiotensin II receptor blocker; CCB = calcium channel blocker.

may be appropriate in certain patient groups – for example, younger patients.[20] In addition, as reported in the recent meta-analysis, Emdin and colleagues considered the increase in target SBP from 130 to 140 mmHg[19,20] to be inappropriate because even though a SBP level of less than 140 mmHg was not associated with better outcomes for CVD or CHD, better outcomes for stroke and progression of albuminuria were observed.[7] Furthermore, although not explicitly reported, there remains an opinion that in subjects with evidence of renal disease, such as increasing albuminuria, aggressive BP targets continue to be worth pursuing.

It should be noted that the most recent Royal Australian College of General Practitioners (RACGP)/Diabetes Australia guidelines still recommends 130/80 mmHg as a BP target for those with type 2 diabetes,[21] which is consistent with the recommendations of Kidney Health Australia.[22] We await a further update of these guidelines, which are likely to be reconsidered with the recent publication of JNC 8,[19] as is mentioned in the RACGP/Diabetes Australia publication *General Practice Management of Type 2 Diabetes, 2014-2015*.[21]

The general view is that treatment of hypertension in subjects with diabetes should be individualised. In addition, the benefits and side effects of treatment should be considered when making decisions about target BP, and the choice of BP lowering medications, as discussed below.

Effects of aggressive blood pressure lowering

Aggressive BP lowering may be associated in some subjects with syncope, dizziness and, rarely, deterioration in renal function. For example, in the ACCORD-BP study serious adverse events attributed to antihypertensive treatment occurred in 77 of the 2362 participants in the intensive-therapy group (3.3%; mean SBP in the group, 119 mmHg).[11] By contrast, in the standard-therapy group, in whom the mean SBP was 134 mmHg, only 30 of the 2371 participants (1.3%; $p<0.001$) reported adverse effects. In another analysis by Australian researchers, major CV outcomes appeared to reach a plateau in patients with type 2 diabetes after attaining a SBP of 140 mmHg.[23]

What is the best way to achieve blood pressure control?

Lifestyle modifications

The treatment of high BP should first emphasise lifestyle modifications, including weight reduction and, although controversial in people with diabetes, potentially, a decrease in salt intake. In the general population, salt reduction has been recommended as an approach to reduce BP; it appears to be effective in achieving reductions of up to 5 mmHg, although there are wide variations in responsiveness. Interestingly, several recent studies in subjects with either type 1 or type 2 diabetes have suggested that severe salt restriction is associated with increased mortality, including CV mortality.[24,25] This phenomenon remains unexplained but may occur as a result of local activation of the RAS.

Long-lasting lifestyle modifications often need a multidisciplinary team approach, and sustainability of these changes is often difficult for patients to maintain. In the Look AHEAD (Action for Health in Diabetes) study, lifestyle intervention for up to 10 years had no benefit on mortality or CV events.[26] Interestingly, the recent renal follow up of this study showed some benefits, including reduced severe chronic kidney disease (CKD) and better BP control.[27]

Choice of first-line treatment

A major issue in the management of hypertension in the setting of diabetes is the choice of first-line antihypertensive treatment (Box 3). No significant differences have been shown among the four major antihypertensive drug classes (ACE inhibitors, ARBs, thiazide-type diuretics and calcium channel blockers [CCB]) in terms of protecting individuals with hypertension from CV events.[28] Thus, it has been suggested that any of the four drug classes could be used as initial treatment in patients with diabetes and hypertension, as outlined in JNC 8;[19] however, the role of diuretics in this setting remains controversial.

The major controversy in the choice of first-line treatment relates to the prevention, attenuation or reversal of renal disease. The landmark Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) trial and Irbesartan Diabetic Nephropathy trial (IDNT) suggested that agents that block the RAS such as ARBs may be superior to other drugs, including CCBs.[29,30] Thus, most guidelines still recommend ARBs or ACE inhibitors as first-line treatment when there is evidence of renal disease. Nevertheless, as noted earlier, the role of these agents in the prevention of diabetic nephropathy in the absence of systemic hypertension is unproven.[12,13]

Choice of second- and third-line treatments

Since most patients with diabetes and hypertension require more than one drug to control BP, it is preferable that an ACE inhibitor or ARB be included in the regimen. However, simultaneous administration of these agents should be avoided. Although early studies demonstrated that this combination reduced BP and albuminuria in type 2 diabetes,[31] subsequent studies with hard endpoints, including development of end stage kidney disease (ESKD), mortality and

CV events, showed no benefit.[32,33] Furthermore, the recently completed Aliskiren Trial in Type 2 Diabetes Using Cardiorenal Endpoints (ALTITUDE) that used an alternative approach to interrupt the RAS (specifically the use of the renin inhibitor aliskiren and the ARB losartan) found that there was no benefit on CVD and an increased risk of hyperkalaemia.[34]

The Avoiding Cardiovascular Events Through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) study,[35] which included a significant number of subjects with type 2 diabetes, randomised individuals already taking an ACE inhibitor to a diuretic or CCB. The group receiving the CCB amlodipine had better outcomes than those receiving the diuretic hydrochlorothiazide. Thus, CCBs are often chosen as the second drug to treat BP in diabetes.

Despite the use of two antihypertensive agents, target BP is often not achieved and triple therapy regimens including a RAS blocker, a CCB and a diuretic are often needed. Fortunately, such combinations are increasingly available as one tablet in a fixed-dose combination. The role of diuretics for BP reduction in subjects with diabetes remains controversial, however, with different recommendations made in the various guidelines.[19,36] Nevertheless, increasingly it is appreciated that diuretics, although not first line, may be needed in subjects with type 2 diabetes and in low doses they do not adversely affect glycaemic control. As there is a lack of clear benefit of diuretics over other antihypertensive agents,[37] however, most clinicians will not use this class as first-line treatment.

Consideration of comorbidities

Type 2 diabetes is a complex condition with many comorbidities, including increased risk of heart failure and peripheral vascular disease. These comorbidities must be considered in the selection of BP lowering agents (Box 3). For example, diuretics may be useful in subjects with or at risk of heart failure whereas beta-blockers should be avoided in those with peripheral vascular disease.

Diagnosing and managing resistant hypertension

International guidelines have defined resistant hypertension as BP that remains above target levels (above 140/90 mmHg) despite effective lifestyle modifications and the simultaneous use of three antihypertensive agents of different classes (one of which is ideally a diuretic) at optimal doses.[36,38] It is important to discriminate between true and apparent resistant hypertension; often a white-coat effect, fluid overload, inadequate dosing of medications, nonadherence to the treatment or hypertension due to the secondary causes leading to an incorrect diagnosis of resistant hypertension.[39] ABPM should be used to diagnose resistant hypertension.[40]

Detailed investigation should be performed in patients with diabetes who are considered to have resistant hypertension in order to exclude causes of secondary hypertension, including obstructive sleep apnoea, Cushing's disease and renovascular causes (Box 2). Renovascular hypertension should be considered in this setting, since renal artery stenosis has been reported to be increased in people with diabetes, presumably as a result of the increased atherosclerotic burden.

Renal denervation, a modern nondrug approach, has recently been considered as an appropriate treatment strategy for resistant hypertension. It involves bilateral destruction of the renal nerves using radiofrequency ablation and may be effective since the sympathetic nervous system has an important role in hypertension.[41] The Renal Sympathetic Denervation in Patients with Treatment-Resistant Hypertension (Symplicity HTN-2) trial, which included a significant number of patients with diabetes, reported this procedure to be an effective and safe method in the treatment of resistant hypertension.[42] However, in the more recent Renal Denervation in Patients With Uncontrolled Hypertension (Symplicity HTN-3) trial no benefits were observed with this procedure.[43] Interestingly, in this latter study, the placebo group was subjected to a sham procedure. It is hoped that subsequent, adequately powered, well-performed renal denervation studies that are currently in the planning stage will help to resolve the role of this procedure in subjects with resistant hypertension, which is often seen in patients with diabetes.

Glucose lowering drugs and blood pressure

Although BP reduction in subjects with diabetes is usually achieved by using classical antihypertensive drugs, certain classes of glucose lowering drugs may directly influence BP. The older agents such as metformin and sulfonylureas have no or minimal effect on BP. Newer agents such as thiazolidinediones do not appear to directly affect BP, but since these peroxisome proliferator activated receptor-gamma (PPAR-gamma) agonists activate the distal sodium transporter (the epithelial sodium channel), they can promote oedema and precipitate heart failure. Dipeptidyl peptidase 4 (DPP-4) inhibitors are increasingly being used in type 2 diabetes;[44] their effects on BP appear to be neutral. By contrast, glucagon-like peptide-1 (GLP-1) analogues may reduce BP by about 1 to 5 mmHg, as reported in a recent meta-analysis,[45] in association with effects on weight loss. The sodium-glucose cotransporter 2 (SGLT2) inhibitors, which promote not only glycosuria but also natriuresis, have been shown to reduce BP by 2 to 5 mmHg.[46,47] Whether the effect of SGLT-2 inhibitors in reducing BP ultimately translates to reduced CVD and renal disease remains to be determined and is the subject of several large ongoing clinical trials.

Conclusion

Hypertension is an important CVD risk factor that needs to be treated appropriately in people with diabetes. Current guidelines have become less stringent in terms of initiation of BP lowering drugs. The advent of new glucose lowering drugs such as SGLT-2 inhibitors provides clinicians with a new opportunity not only to improve glycaemic control but also to have the added benefit of reducing BP. **ET**

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A list of references is included in the website version of this article (www.medicinetoday.com.au).

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