



Game changers in type 2 diabetes

After three antihypertensives, what's next?

PAT PHILLIPS MB BS, MA(Oxon), FRACP, MRACMA, GradDipHealthEcon(UNE)

Hypertension is an important risk factor for both micro- and macrovascular complications in people with type 2 diabetes, and can be difficult to control. The clinical scenario of uncontrolled hypertension despite three antihypertensive medications is not uncommon.

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Hypertension is often difficult to control in patients with diabetes and in most cases an average of three to four different antihypertensive medications are required to achieve the target blood pressure of 130/80 mmHg or below.¹ The first three antihypertensive medications should be chosen because they have different mechanisms of action, the recommended choice for patients with type 2 diabetes being between angiotensin-converting enzyme (ACE) inhibitors/angiotensin II receptor antagonists, thiazide diuretics and dihydropyridine calcium channel blockers.²⁻⁴ Beta blockers are an alternative to calcium channel blockers in patients with a history of myocardial infarction, heart failure, coronary artery disease, or stable angina, because of their effect of reducing cardiovascular events.⁵ If control of hypertension is not achieved with three agents in combination, the next step is more difficult (for both doctor and patient), and the situation may indicate that there is some underlying cause or contributor to the hypertension.

This article reviews the potentially remediable causes of and contributors to hypertension in people with type 2 diabetes, and offers some practical suggestions for management. It is the fourth in a series of articles reviewing clinical situations that indicate a

Dr Phillips is a Consultant Endocrinologist at the QE Specialist Centre, Adelaide, SA.

FACTORS INCREASING RISK OF HYPERTENSION AND COMPLICATING MANAGEMENT

- Age over 65 years
- Obesity (body mass index above 30 kg/m²)
- Unhealthy lifestyle (particularly low physical activity and high sodium consumption)
- Renal impairment
- Therapeutic inertia in doctors and patients (reluctance to add further medication to current therapy)
- Nonadherence to medications prescribed (or management recommendations)

major change in the level of risk of diabetes-related complications and prompt the need for major review of diabetes management.

DIABETES AND HYPERTENSION – DOUBLE TROUBLE

Hypertension is an important but frequently underestimated health issue in the general population, being common and often uncontrolled (and becoming harder to control), given the ageing, unhealthy lifestyle and increasing obesity of the general population. Hypertension is particularly important in people with type 2 diabetes because it is more common, less well-controlled and more difficult to manage than in patients without diabetes.⁶

Type 2 diabetes is associated with all of the factors that make hypertension more common and more difficult to manage in the general population (see the box on this page). These associations may underlie the observation that hypertension is more common, less often treated and, if treated, less often controlled in people with diabetes than in the general population. Hypertension is also associated with a greater cardiovascular risk in people with diabetes, with the National Heart Foundation of Australia suggesting that

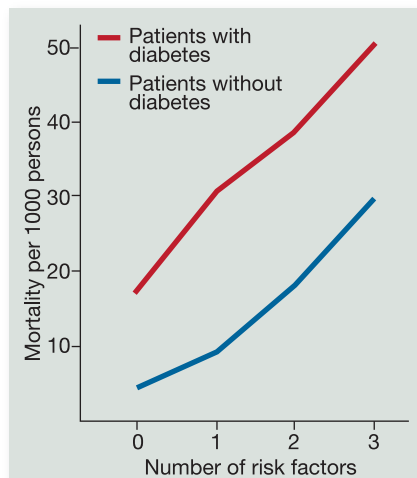


Figure 1. Cardiovascular mortality, risk factors (hypertension, dyslipidaemia, smoking) and type 2 diabetes.⁷

the risk level in those with diabetes is increased one level over and above the risk estimated from the usual risk factors.

Although the relative risk of a cardiovascular event from uncontrolled hypertension may be the same in people with and without diabetes, the absolute risk increase is much higher in those with diabetes because of the already high background risk associated with type 2 diabetes (Figure 1).⁷ Type 2 diabetes is also often referred to as a ‘coronary equivalent’ – that is, a person with diabetes has the same risk of a cardiovascular event as someone without diabetes who has already had a coronary event.

The United Kingdom Prospective Diabetes Study (UKPDS 38) showed that hypertension is an independent risk factor in people with type 2 diabetes for the microvascular complications of nephropathy and retinopathy, as well as for macrovascular complications.⁸

The bottom line is that hypertension is an important risk factor for both micro- and macrovascular complications in people with type 2 diabetes, and can be very difficult to control. The clinical scenario of uncontrolled hypertension despite three antihypertensive medications is not uncommon.

CAUSES OF AND CONTRIBUTORS TO HYPERTENSION

When the use of three antihypertensive agents in combination is no longer effective in achieving the desired control of blood pressure in any person, potentially reversible causes and contributing lifestyle factors should be reviewed before considering the next steps to take (Table 1).

Blood pressure measurement

Errors in measurement, either in the technique used or for other reasons, should be suspected as a cause of hypertension in patients with no or minimal end organ damage.

Two common mistakes in performing measurements are to not let the patient sit quietly for at least five minutes beforehand and to use a cuff that is too small.⁵

White-coat hypertension occurs in 20 to 30% of the general hypertensive population.⁹ If it is suspected, 24-hour ambulatory or self-monitoring blood pressure profiles should be obtained.

Calcified arteries are another cause of spuriously high blood pressure readings, because such arteries resist compression. Elevated Doppler ankle brachial pressure indices (above 1.3) suggest calcified non-compressible arteries; low values (below 0.9) suggest peripheral vascular disease.

Medication use

Nonadherence with antihypertensive medications occurs in about 40% of the general hypertensive population, and probably in a greater proportion of those with diabetes because of the associated high medication burden.¹⁰ Checking that prescriptions have been written and filled can help identify cases of nonadherence, as can arranging a Home Medications Review, which will also check for interfering medications.

Other medication (prescription, over-the-counter and alternative/complementary) often interferes with the antihypertensive effect of prescribed medication (see the box on page 49). In particular, NSAID use is common, and

COMMONLY USED MEDICATIONS INTERFERING WITH BLOOD PRESSURE CONTROL*⁹

- Analgesics: NSAIDs (including aspirin and selective COX-2 inhibitors)
- Sympathomimetic agents (decongestants, diet pills, cocaine)
- Stimulants (amphetamine and derivatives)
- Oral contraceptive pills
- Alternative/complementary medications (e.g. ephedra, ma huang)

* Less commonly used medications include cyclosporin, erythropoietin and natural liquorice.

may not be reported by the patient, especially if the NSAID is obtained over-the-counter. A Home Medications Review may help identify a person using NSAIDs, who then can be counselled to use alternative means to, for example, limit musculoskeletal discomfort (such as weight reduction, exercise and use of paracetamol). Another good reason for people with diabetes to avoid using NSAIDs is that they further increase cardiovascular risk in an already high cardiovascular risk group, and can impair renal function.

Lifestyle factors

'Eat less, drink moderately, walk more and sleep well and you will live to 100' is not a bad prescription for a general population who is likely to be overweight, overimbibing, underactive and nocturnally apnoeic, and possibly also eating a high-salt diet. Lifestyle change is difficult to achieve and even more difficult to maintain, but with help from a psychologist, dietician and exercise physiologist through a Team Care Arrangement some patients with hypertension may be motivated and able to modify their lifestyle.

Identifying and reversing any lifestyle factors contributing to hypertension helps in its reduction, and the more factors that are improved, the better. Benefits of lifestyle improvements in terms of blood

TABLE 1. INVESTIGATIONS FOR CAUSES OF AND CONTRIBUTORS TO HYPERTENSION

Recommended investigations	Rationale and notes
In most people with hypertension	
End organ damage	Absence suggests measurement error
• Fundoscopy	To identify vascular changes, haemorrhages or exudates
• Renal impairment	To detect albuminuria and/or elevated plasma creatinine level
• ECG	To identify left ventricular hypertrophy and unrecognised myocardial infarction
• Echocardiogram	To identify left ventricular hypertrophy and left ventricular dysfunction
Sleep apnoea	
• Epworth Questionnaire	Simple 10-item questionnaire
• Sleep study	Inpatient or home
In some people with hypertension	
Adrenal disorders	
• Aldosterone/renin ratio	To identify primary hyperaldosteronism (good negative predictive value)*
• Plasma metanephrine	To detect pheochromocytoma (if symptomatic)
• 24-hour urine cortisol	To detect Cushing's syndrome (if clinical picture suggestive) [†]
Rarely in people with hypertension	
Thyroid/parathyroid disorders	
• Thyroid function tests	To detect hypo/hyperthyroidism
• Plasma calcium/parathyroid hormone	To detect hyperparathyroidism
Artery-related conditions	
• Radionuclide renal scanning (technetium-labelled MAG3)	To detect renal artery stenosis
• Blood pressure measurement	Disparities in blood pressure between right and left arms or upper and lower limbs suggests aortic coarctation – consider referral

ABBREVIATION: MAG3 = mercaptoacetyltriglycine.

* A negative aldosterone/renin ratio has a high negative predictive value for primary hyperaldosteronism.

[†] For example, recent progressive onset, abdominal striae, osteoporosis, central obesity.

pressure reduction achieved are summarised in Table 2.¹¹⁻¹⁶

Sleep apnoea is common in people with a body mass index above 30 kg/m² or

neck circumference greater than 42 cm. The Epworth Sleepiness Scale questionnaire (available online at: <http://epworthsleepinessscale.com>) is a useful screen for

TABLE 2. EFFECT OF LIFESTYLE MODIFICATION ON BLOOD PRESSURE¹¹⁻¹⁶

Lifestyle measure	BP reduction (systolic/diastolic; mmHg)*
Weight loss (10 kg) ¹¹	6/5
Salt intake (<100 mmol/day) ¹²	5-10/2-9
Alcohol consumption (nil) ¹³	7/7
Activity (aerobic, 30 min/day) ¹⁴	4/3
Diet (DASH) ¹⁵	11/6.5
Use of continuous positive airway pressure ¹⁶	0-14/0-10

* Rounded to the nearest unit.

† The Mediterranean Diet Study (DASH = Dietary Approaches to Stop Hypertension).

sleep apnoea, and sleep investigations – either inpatient sleep studies or home sleep studies – will identify patients who might benefit from continuous positive airway pressure therapy.

Most people with diabetes and hypertension could benefit from lifestyle advice, and adherence and persistence with lifestyle change could mean that uncontrolled hypertension becomes controlled and that some antihypertensives could be stopped.

Secondary causes

Secondary hypertension is less likely to be the reason for difficult to control hypertension than are blood pressure

measurement errors, medication non-adherence, medication interference or lifestyle factors. Secondary causes of hypertension include endocrine organ-related (adrenal and thyroid/parathyroid) and artery-related (renal and aortic) conditions.

Primary hyperaldosteronism has been found in as many as 20% of those requiring three or more medications.¹⁷ The aldosterone to renin ratio is an effective screening test for primary hyperaldosteronism, even with concurrent hypotensive medication (excluding potassium-sparing medications), and has a high negative predictive value.¹⁸ Pheochromocytoma and Cushing’s syndrome are less likely

endocrine-related causes of secondary hypertension but should be considered in patients with suggestive clinical pictures.

Renal artery stenosis is common in young people with hypertension and also in older people with type 2 diabetes and renovascular disease. Although medical therapy may still be preferable to surgery for this condition, it is useful to identify the cause of the resistance to therapy and to intensify medication targeting the renin-angiotensin-aldosterone axis. Plasma renin activity or concentration may be elevated, and radionuclide renal scanning using technetium-labelled MAG3 (mercapto-acetyltriglycine) is a safe method of assessment. Coarctation of the aorta as a cause of resistant hypertension is more common in young people but suspicion in older people (discrepancy in blood pressure between right and left arm or between upper and lower limbs) may prompt referral to a hypertension specialist.

ESCALATING ANTIHYPERTENSIVE MEDICATION

Having excluded or corrected as far as possible causative and/or contributing factors for hypertension in a patient taking three antihypertensive agents in combination, the next stage in controlling hypertension is to decide whether to escalate antihypertensive medication. The

TABLE 3. OPTIONS FOR ESCALATING ANTIHYPERTENSIVE MEDICATION

Additional antihypertensive options	Major disadvantages
1. Increase dose of current medications (especially thiazide diuretic)	Increased side effects for lower efficacy
2. Then add a calcium channel blocker or a β-blocker,* whichever has not yet been used	Peripheral oedema (calcium channel blocker); dyslipidaemia (beta blocker)
3. Then add mineralocorticoid blockade (amiloride, triamterene, eplerenone or spironolactone), or	Hyperkalaemia
Add an α-blocker (prazosin or terazosin), or	Postural hypotension, heart failure†
Add a central sympatholytic (clonidine or moxonidine), or	Postural hypotension, depression
Add an ACE inhibitor or angiotensin II receptor antagonist, whichever has not yet been used	No better blood pressure control; greater side effects

* Atenolol is not associated with all the clinical benefits of other beta blockers and may not reduce central blood pressure as much.

† Identified for doxazosin (of the same class) in ALLHAT Trial (JAMA 2000; 283: 1967-1975).

increased benefits from additional medication tend to be less than the increase in ill effects (including decreased medication adherence), and the assistance of a colleague with a special interest in diabetes or hypertension may be useful.

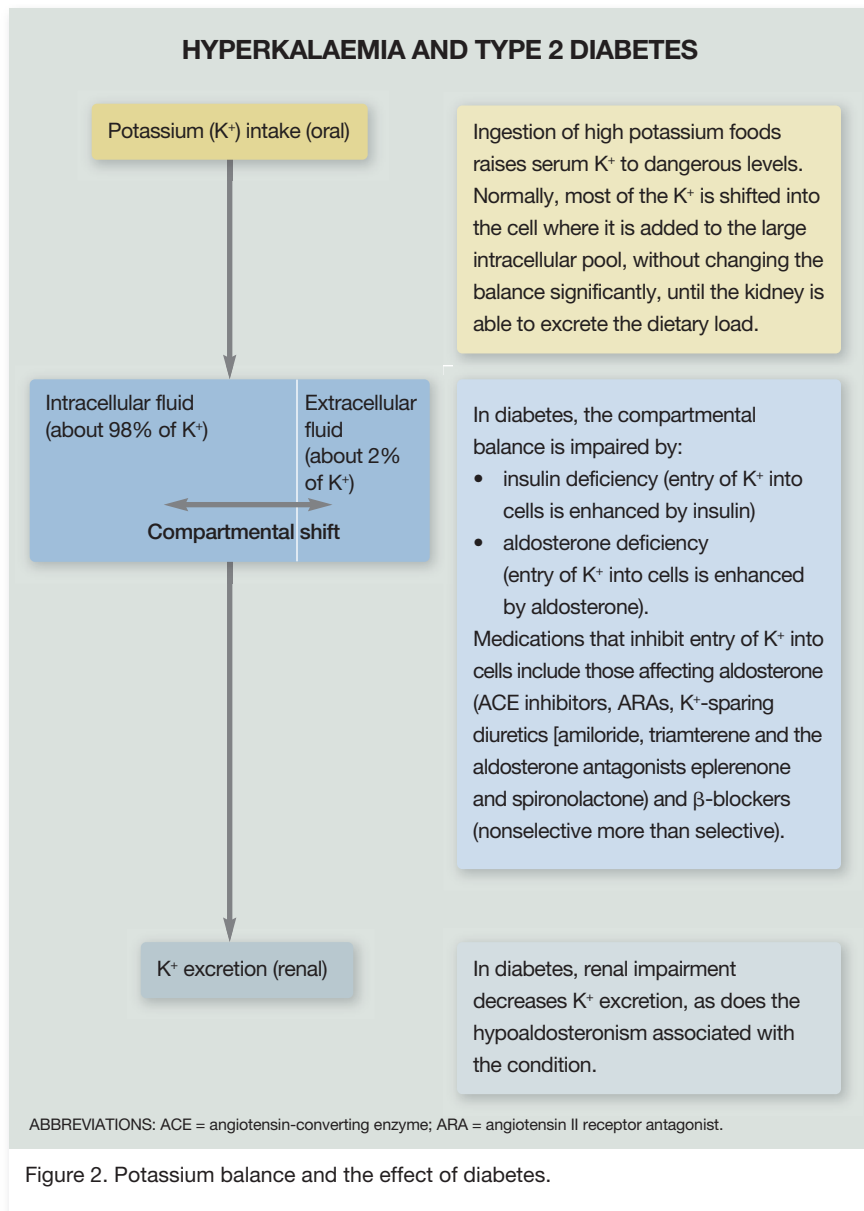
If medication escalation is indicated, the steps listed below seem to be the next to take, although each of these options has its own particular disadvantages (Table 3).

1. Increase the dose of current medications (especially the thiazide diuretic).
2. Then add whichever of a dihydropyridine calcium channel blocker or β -blocker has not yet been used.
3. Then add a mineralocorticoid blocker (a potassium-sparing diuretic or an aldosterone antagonist), an α -blocker or a sympathomimetic blocker, or increase renin–angiotensin–aldosterone blockade by using both an ACE inhibitor and an angiotensin II receptor antagonist.

Some of these options may be possible without increasing medication burden (i.e. by increasing the dose or using combined preparations – single-pill combinations of two or three antihypertensive agents are available, with the agents in varying doses).

In people with longstanding type 2 diabetes, beta cell function and the insulin response to hyperkalaemia may be lost. Several antihypertensive agents (ACE inhibitors, angiotensin II receptor antagonists, mineralocorticoid blockers and other potassium-sparing diuretics) affect the renin–angiotensin–aldosterone system and the renal excretion of potassium (Figure 2). Hyperkalaemia is yet another reason to avoid the use of NSAIDs, as these also affect renal potassium excretion. Other antihypertensive agents (non-selective β -blockers, mineralocorticoid blockers and other potassium-sparing diuretics) affect compartmental potassium balance.

In the future, interventions such as catheter-based renal denervation and electrical stimulation of carotid baroreceptors may become available as non-



medication-based strategies for difficult to control hypertension.

CHECKING THE OTHER ABCS

The high cardiovascular risk associated with the ‘double trouble’ of diabetes and hypertension makes it important to manage people with type 2 diabetes as well as possible by achieving the management targets for glycosylated haemoglobin (A_{1c}), blood pressure, cholesterol and smoking (the ABCs of diabetes care), as shown in

Table 4.³ It may not be possible to get the blood pressure right on target but reaching the target for one of the other risk factors may be more achievable.

A GP Management Plan and Team Care Arrangement gives the doctor and the patient opportunities to review professional and self-care respectively, as well as medication, and to see if there are opportunities to improve the risk profile by shifting one or more of the ABCs closer to target.

TABLE 4. MANAGEMENT TARGETS IN TYPE 2 DIABETES: THE ABCS OF DIABETES CARE*³

Factor	Target
A – Glycosylated haemoglobin (A _{1c})	<7.0% (< 5 mmol/mol)
B – Blood pressure	<130/80 mmHg
C – Cholesterol [†]	<4 mmol/L
s – Smoking	0

* A further 's' (salicylate therapy) in the original ABCs is no longer routinely recommended for those people with diabetes and no known cardiovascular disease.
[†] LDL cholesterol <1.8 mmol/L in the presence of existing coronary artery disease (angina, history of myocardial infarction).

CONCLUSION

Hypertension is an important risk factor for both microvascular and macrovascular complications of diabetes and people with type 2 diabetes and uncontrolled hypertension have a greater absolute risk of a cardiovascular event than those without diabetes. Hypertension is often difficult to control in people with diabetes, and a combination of several different antihypertensive medications is usually required to achieve the target blood pressure of 130/80 mmHg or less.

If blood pressure targets cannot be reached with the first recommended antihypertensive agents in combination, potentially reversible causes of hypertension (including secondary causes) and contributing lifestyle factors should be reviewed before considering the next steps to take. Escalation of antihypertensive medication involves the steps of increasing the dose of current medications; then adding a dihydropyridine calcium channel blocker or β -blocker, whichever has not yet been used; and then adding a mineralocorticoid blocker, an α -blocker or a sympathomimetic blocker, or increasing renin-angiotensin-aldosterone blockade by using both an ACE inhibitor and an angiotensin receptor antagonist.

It may not be possible to achieve the blood pressure target in a particular patient, but reaching the target for one of the other diabetes risk factors (i.e. for A_{1c}, cholesterol and smoking) may be

more attainable and/or beneficial than escalation of antihypertensive therapy. **MT**

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