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Adults with diabetes

Pharmacological management of hypertension

Cardiovascular and renal disease are leading causes of morbidity and mortality in patients with diabetes.[1] Hypertension is an independent risk factor for both macrovascular (stroke, myocardial infarct, peripheral vascular disease) and microvascular (nephropathy, neuropathy, retinopathy) complications, and is a common co-existing condition in diabetes.[2,3]

People with diabetes are considered to be at high or very high risk of a cardiovascular event. Aboriginal people and Torres Strait Islanders are at high risk of developing diabetes and a cardiovascular event,[4] and of developing end stage renal disease, therefore careful control of blood pressure (BP) is vital. The absolute risk of cardiovascular disease (CVD) in any individual is determined by a complex interplay of many risk factors. A commonly used cardiovascular risk calculator is the New Zealand Risk Calculator, available at www.nzgg.org.nz. Another useful, diabetes specific calculator is the UKPDS risk engine, available at www.dtu.ox.ac.uk/riskengine/.

Early, intensive, long term interventions targeting multiple risk factors for CVD in those with diabetes significantly reduce the risk of macro- and micro-vascular complications. This was demonstrated in a primary prevention trial (the Steno-2 study), which targeted hypertension, aspirin therapy, hyperglycaemia, microalbuminuria, hyperlipidaemia, smoking, and sedentary lifestyle in patients with diabetes and microalbuminuria. The study reported a 50% reduction in the number of micro- and macro-vascular events over a period of 7.8 years (absolute risk reduction: 20–32%; NNT: 3–5).[5]

Hypertension

Approximately 70% of patients with diabetes will develop hypertension compared to 20% of patients without diabetes.[6] Effective treatment of hypertension for patients with diabetes reduces both macro- and micro-vascular complications.[2,3] Benefits have been established for patients with diabetes without hypertension who achieve even lower BP (slowed progression to incipient and overt diabetic nephropathy, reduced progression of diabetic retinopathy and lower incidence of stroke).[7]

The target BP for patients with diabetes and no signs of diabetic nephropathy is <130/80 mmHg.[2,3,8–10] For patients with diabetic nephropathy with proteinuria of >1 g/day, the target is <125/75 mmHg.[2,4,8,11,12] Blood pressure should be measured at every visit and as a minimum every 6 months.[13] More frequent monitoring will be required if BP is poorly controlled or when making changes to antihypertensive medication regimens.

Both lying and standing BP should be assessed, as diabetic patients with autonomic neuropathy are prone to orthostatic hypotension.[8,12] The benefits of lowering BP to target should be weighed in each individual against the risk of postural hypotension and falls. The approaches to BP management and target levels are the same for type 1 and type 2 diabetes.

Alcohol, NSAIDs (including selective COX-2 inhibitors), sibutramine, corticosteroids, oral decongestants, monoamine oxidase inhibitors (MAOIs), venlafaxine and cyclosporin, may all increase BP.[13] Some complementary medicines may also increase BP.

Lifestyle

Nonpharmacological treatments, particularly maintenance of ideal weight, regular exercise and minimisation of salt and alcohol in the diet, can be trialled before pharmacotherapy in many cases. In any event, a healthy lifestyle should always support pharmacotherapy.[2]

Choice of antihypertensive agent

The cardiovascular benefits of BP control for patients with diabetes have been demonstrated with angiotensin converting enzyme inhibitors (ACEIs), angiotensin II receptor antagonists (ARAs), low dose thiazide diuretics, beta blockers and calcium channel blockers (CCBs).[2,3,8]

Table 1. Pharmacological management of BP in diabetes (type 1 or type 2)[13]

Make the diagnosis and consider BP targets	BP <130/80 mmHg if no diabetic nephropathy present BP <125/75 mmHg if proteinuria >1g/day	Ambulatory BP monitors can provide information over a 24 hour period. This may be useful in 'white coat' hypertension or in refractory hypertension Any reduction of BP toward target is likely to be beneficial. While attempting to reach target BP is important, reductions in BP without reaching target should not be considered as failure of therapy Postural hypotension is common in people with diabetic autonomic neuropathy. May need to accept that BP target unable to be met as a compromise to prevent causing a fall through postural hypotension
Encourage a healthy lifestyle	Healthy eating (particularly reduced salt intake and moderate alcohol intake) Maintain normal weight Regular exercise	Lifestyle changes may often be tried before pharmacotherapy and should support pharmacotherapy if instituted
Use a first line pharmacological agent	ACEI (or ARA if ACEI is not tolerated) unless contraindicated	These agents have demonstrated cardiovascular and renal benefits in diabetes
Consider an alternative agent if an ACEI or ARA cannot be used	Low dose thiazide diuretic or Calcium channel blocker or Beta blocker	Choice of agent may depend on co-existing conditions and potential for drug interactions and adverse effects. For example, a beta blocker may be selected if the patient has comorbidities such as angina or previous myocardial infarction
Review BP control	Allow at least 4 weeks to assess response to therapy unless there is an urgent indication to reduce BP	Combination therapy will often be needed to reach BP goals Consider a second agent if further lowering of BP is needed
Add a second agent if target BP not met		As above, the choice of agent may depend on comorbidities and potential for drug interactions and adverse effects
Consider a third agent if further lowering of BP is needed		As above, the choice of agent may depend on co-morbidities and potential for drug interactions and adverse effects

Angiotensin converting enzyme inhibitors have a beneficial effect on cardiovascular and renal function; ARAs have a role where ACEIs are indicated but not tolerated, and for those with albuminuria.[2]

When selecting an antihypertensive drug, consider possible effects on coexisting conditions. Concurrent therapy with more than one drug will often be needed to achieve BP targets.[1–3,8,13] Using concurrent therapy at low doses can maximise effectiveness and minimise adverse effects.[4,8,9]

Angiotensin converting enzyme inhibitors

For patients with diabetes, ACEIs are often advocated as first line therapy because of coexisting conditions:

- micro- or macro-albuminuria[1–4,11,13]
- postmyocardial infarction[2,4,8,13,14]
- left ventricular dysfunction[10,13,14]
- heart failure.[2–4,13,14]

Angiotensin converting enzyme inhibitors reduce progression from microalbuminuria to overt nephropathy for both normotensive and hypertensive patients with diabetes.[2,15] Serum potassium and renal function should be assessed before commencing an ACEI (or ARA). It is quite common for serum creatinine to increase after the initiation of an ACEI. Despite this, continued treatment can lead to long term preservation of renal function. Monitoring is important, and treatment may need to be ceased if there is a substantial acute increase, or sustained elevation, of the serum creatinine.

Angiotensin II receptor antagonists

Angiotensin II receptor antagonists are an alternative for patients who cannot tolerate an ACEI (eg. because of cough).[1,2,8,9,15] Angiotensin II receptor antagonists reduce BP to a similar extent to ACEIs and have been shown to slow progression from micro- to macro-albuminuria and of macroalbuminuria to end stage renal failure, cardiovascular events or death.[2,16]

Low dose thiazide diuretics

Low dose thiazide diuretics may be used in the treatment of hypertension in patients with diabetes, particularly in the absence of renal disease.[1,8,9] Effects on glucose tolerance and plasma lipids are

minimal with current recommended low doses.[13] A low dose thiazide may be effectively combined with other antihypertensive agents (ACEI, ARA, beta blocker, CCB) to achieve target BP goals. The majority of patients will require more than one agent to achieve BP targets.

Beta blockers

Beta blockers may be used in patients with diabetes[13] with attention to tight glycaemic control and lipid levels. They are an acceptable option in people with diabetes, particularly in the presence of coexisting CVD such as heart failure, angina or myocardial infarction.[4] Beta blockers may mask important signs of acute hypoglycaemia such as tachycardia and tremor (particularly in type 1 diabetes) and may increase the incidence and severity of hypoglycaemia, although this has not been unequivocally established. Selective beta blockers such as atenolol and metoprolol may produce less alteration of glucose metabolism and may be preferred in diabetes.[13]

Calcium channel blockers

Calcium channel blockers have no adverse effects on glucose tolerance and may be used if first line treatments cannot be employed. Diltiazem and verapamil have the greatest effect on reducing cardiac output, and the dihydropyridines (eg. amlodipine) act by reducing peripheral resistance.[13] Long acting or sustained release preparations are preferred.[2]

Other drugs

A number of other drug classes, such as the centrally acting antihypertensives (clonidine, methyldopa, moxonidine) and the selective alpha blockers (prazosin, terazosin) are still used, but there is no reliable evidence from randomised trials about their beneficial effect on cardiovascular outcomes.[13] Alpha blockers are no longer considered as first line agents for the management of hypertension. The doxazosin (an alpha blocker) arm of a large antihypertensive trial was discontinued early because of an excessive occurrence of heart failure.[17]

Response to treatment

Allow at least 4 weeks to gauge response to treatment, unless there is an urgent indication to reduce BP (eg. malignant or accelerated hypertension, dissecting aortic aneurysm).[13]

Further information

For drug information including precautions, adverse effects, interactions and contraindications, please refer to the *Australian Medicines Handbook* and approved product information.[1]

A summary of the steps involved in the pharmacological management of hypertension in diabetes is provided in *Table 1*.

Conflict of interest: none.

Acknowledgment

The Department of Veterans' Affairs Veterans' MATES Program is provided by the University of South Australia, Quality Use of Medicines and Pharmacy Research Centre in association with Discipline of General Practice, University of Adelaide; Discipline of Public Health, University of Adelaide; Repatriation General Hospital, Daw Park; National Prescribing Service; Australian Medicines Handbook; Drug and Therapeutics Information Service.

Acknowledgment and disclaimer

This work has been produced with the assistance of funding provided by the Department of Veterans' Affairs. However, the views expressed in this version of the work do not necessarily represent the views of the Minister for Veterans' Affairs or the Department of Veterans' Affairs. The Commonwealth does not give any warranty nor accept any liability in relation to the contents of this work.

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