Combining Antihypertensives in People with Diabetes

The majority of people with diabetes will develop hypertension and this subsequently increases the risk of microvascular and macrovascular complications. In fact, 80% of people with diabetes will die as a result of a vascular event.[1]

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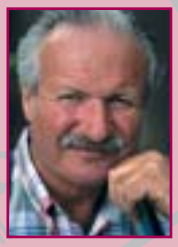
Blood pressure (BP) control has been shown to significantly reduce the risk of microvascular and macrovascular complications and all-cause mortality.[2,3] Also, greater improvements in cardiovascular outcomes can be achieved in patients with diabetes than in patients without.[4] Therefore, although people with diabetes are at an increased risk, the benefits of treatment are even greater than in the general population.

The first priority for patients with diabetes should be vascular protection to decrease cardiovascular risk. The Canadian Diabetes Association (CDA) Clinical Practice Guidelines recommend a multifaceted approach to vascular protection, which includes:

- treatment with an angiotensin-converting enzyme (ACE) inhibitor,
- antiplatelet therapy,
- glycemic control,
- lifestyle modifications,
- smoking cessation and
- lipid and BP control.[5]

The optimum BP target for people with diabetes is < 130/80 mmHg. Achieving this BP target, which is also the threshold for treatment initiation,[5,6] usually requires the use of several antihypertensive agents.

Bill's medical history



Bill, 69, Caucasian, presents with the following medical history:

- Type 2 diabetes
- Hypertension
- Dyslipidemia
- Myocardial infarction (MI).

For Bill's lifestyle, see page 38

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Diabetes and normal urinary albumin excretion (< 30 mg/day)

First-line treatment options for hypertensive patients with diabetes and normoalbuminuria are ACE inhibitors, angiotensin II receptor blockers (ARBs) or thiazide diuretics. As vascular protection is the first priority in the optimal management of patients with diabetes, most should be started on an ACE inhibitor. In the Heart

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Bill's lifestyle and medications

- For the last 54 years, Bill has smoked a pack a day.
- He does not drink.
- He has no known drug allergies.
- Bill does have a drug plan. His current medications include:
  - ramipril 10 mg od
  - atenolol 50 mg od
  - glyburide 5 mg bid
  - metformin 500 mg tid
  - enteric-coated acetylsalicylic acid 81 mg od
  - atorvastatin 10 mg od.

For more on Bill, see page 41

Outcomes Prevention Evaluation trial (HOPE), the ACE inhibitor, ramipril, 10 mg once per day, was found to decrease the risk of stroke, MI and cardiovascular death by 25% compared to placebo, despite similar BP control in the two treatment arms.[7]

Diabetes and albuminuria (urinary albumin excretion rates > 30 mg/day)

ACE inhibitors and ARBs have the added advantage of decreasing urinary albumin excretion independent of lowering BP and are first-line treatments in patients with a urinary albumin excretion rate > 30 mg/day.

Achieving a BP target of < 130/80 mmHg should be a goal for all patients with diabetes, and this usually requires the use of multiple antihypertensive agents.

Table 1

Side-effects and drug interactions for ACE inhibitors and ARBs

	ACE inhibitors	ARBs
Side-effects	• Hyperkalemia • Cough • Angioedema • Increase in • serum creatinine*	• Hyperkalemia • Angioedema • Increase in serum creatinine*
Drug interactions	• Increased risk of hyperkalemia with potassium-sparing diuretics (triamterene, amiloride), potassium supplements, cotrimoxazole and aldosterone antagonists (spironolactone) • Increased risk of rise in serum creatinine if used with NSAIDs	

* An increase in serum creatinine is expected following initiation or dose increase of an ACE inhibitor or ARB. This is a hemodynamic response due to decreased intraglomerular pressure resulting in a decreased glomerular filtration rate. A serum creatinine rise of up to 30% above baseline is considered acceptable.

ARB: Angiotensin II receptor blocker
NSAIDs: Nonsteroidal anti-inflammatory drugs

Q What monitoring is required when using ACE inhibitors or ARBs?

A As with all antihypertensives, it is important to monitor for efficacy, side-effects, adherence and drug interactions (Table 1).

Combination Therapy

Many patients with diabetes will require more than one antihypertensive agent to reach their BP target. When adding an antihypertensive agent, it is important to consider patient comorbidities, patient tolerance, allergies and the mechanisms of action of the agents. Choosing an antihypertensive agent that will lower BP and treat a patient's comorbid condition is

Table 2
Compelling indications of antihypertensives[6,8]

Compelling indication	Diuretic	ß blocker	ACE inhibitor	ARB	CCB	Aldosterone antagonist
Heart failure	√	√	√	√		√
Post MI		√	√			
Angina		√	√		√ (2nd line)	
CKD			√	√		
Recurrent stroke prevention	√		√			

ARB: Angiotensin II receptor blocker CCB: Calcium channel blocker CKD: Chronic kidney disease
MI: Myocardial infarction

very beneficial and may reduce the number of medications the patient requires. Table 2 outlines compelling indications for the various antihypertensives.

Q *Should an ARB be added to a patient's regimen if they are already taking an ACE inhibitor?*

A Evidence supports the additional antihypertensive effect of this combination. This combination will also reduce urinary albumin excretion in patients with diabetic nephropathy. ACE inhibitors and ARBs may be used for their antiproteinuric effects, even if the patient is at their optimal BP target.

Diuretics

Diuretics are an excellent choice as add-on therapy, since they improve the effectiveness of other antihypertensives, especially ACE inhibitors and ARBs. Patients with diabetes and/or renal disease often have extracellular fluid volume expansion, which can be managed by the addition of a diuretic. For patients with chronic kidney disease, diuretics also help prevent hyperkalemia by increasing potassium excretion.

Q *Which diuretic should be used as add-on therapy?*

A Thiazide diuretics are considered first-line antihypertensive agents because they are generally safe and inexpensive and they have been shown to decrease cardiovascular morbidity and mortality. They are also more effective antihypertensive agents than loop diuretics. Examples of thiazide diuretics include, hydrochlorothiazide, chlorthalidone and indapamide.

Q *When should loop diuretics be used?*

A For patients with renal impairment, specifically with a creatinine clearance rate < 30 mL/minute, a loop diuretic, such as furosemide, is often required. Loop diuretics provide a greater reduction in extracellular

Table 3

Side-effects and drug interactions for dihydropyridine and nondihydropyridine CCBs

	Dihydropyridines	Nondihydropyridines
Side-effects	• Flushing • Headache • Peripheral edema	• Bradycardia • Constipation
Drug interactions	• Grapefruit juice leads to increased drug concentrations	• Increased drug concentrations for drugs that are metabolized by cytochrome P450 3A4 (*e,g.*, cyclosporine, tacrolimus, cinacalcet, statins) • Digoxin: verapamil increases digoxin concentration • Beta-blockers: increased risk of bradycardia and AV block • Grapefruit juice: increased drug concentration of verapamil

fluid volume compared to thiazide diuretics and may be necessary in patients with heart failure. A combination of loop and thiazide diuretic may be used for additive effect.

Q *Is there a role for potassium-sparing diuretics?*

A Potassium-sparing diuretics (amiloride, triamterene) should only be used if the patient is considered at a high risk for hypokalemia. Moreover, they should be used cautiously in patients with renal impairment. Potassium-sparing diuretics may increase the risk of hyperkalemia when combined with ACE inhibitors, ARBs, aldosterone antagonists, cotrimoxazole, nonsteroidal anti-inflammatory drugs (NSAIDs) and potassium supplements.

Calcium-channel blockers

Dihydropyridine calcium channel blockers (CCBs) are primarily vasodilators (*e.g.*, amlodipine, felodipine and nifedipine). Nondihydropyridines, (*e.g.*, verapamil and diltiazem), directly block the atrioventricular node, decrease heart rate, decrease cardiac contractility and have some vasodilatory effects.

Q *What patient characteristics determine whether a dihydropyridine vs. a nondihydropyridine CCB is used in the management of hypertension?*

A Heart rate is an important patient characteristic to consider. Nondihydropyridines decrease heart rate compared to dihydropyridines, which have no effect on heart rate, or increase heart rate, as is the case with nifedipine. Nondihydropyridines should be used cautiously with beta-blockers due to the risk of atrioventricular block. These agents should also be avoided in patients with abnormal systolic left ventricular function. For patients with diabetes and albuminuria, a nondihydropyridine is preferable, as these agents decrease urinary albumin excretion rate.

Q *What monitoring is required for the optimal use of CCBs?*

A See Table 3.

Beta-blockers

Beta-blockers are not indicated as first-line therapy in patients with diabetes. They may be used as

Table 4

Properties of individual beta-blockers

Agent	Relative ß$_1$ selectivity	Intrinsic sympathomimetic activity	Lipid solubility
Acebutolol	++	+	Moderate
Atenolol	++	0	Low
Bisoprolol	++	0	Low
Metoprolol	+	0	Moderate to high
Propranolol	0	0	High

add-on therapy, particularly if the patient has another indication for a beta-blocker as outlined in Table 2.

Beta-blockers differ in terms of their cardioselectivity, lipid solubility and intrinsic sympathomimetic activity. Cardioselective beta-blockers have a greater affinity for ß$_1$ receptors located in the heart and kidney compared to ß$_2$ receptors, which are located in the lungs, pancreas, liver and arteriolar smooth muscle. The degree of lipid solubility determines the extent to which these agents pass the blood brain barrier, but there is conflicting information on whether or not this is clinically relevant. Agents with intrinsic sympathomimetic activity have partial agonist activity at the ß receptor. These agents may not be as protective against cardiovascular events as other beta-blockers. Table 4 outlines the properties of individual agents.

Q Should patient comorbidities affect the choice of beta-blocker?

A Cardioselective beta-blockers are less likely to cause bronchospasm and vasoconstriction. As insulin secretion and glycogenolysis are adrenergically mediated through the ß$_2$ receptor, cardioselective beta-blockers are less likely to cause hyperglycemia or blunt recovery from hypoglycemia in patients with diabetes.

More on Bill

Bill's physical examination shows:

- BP = 155/95 mmHg (sitting and standing)
- Heart rate = 60 bpm
- Jugular venous pressure = 3 cm above the sternal angle
- Mild pedal edema
- Body weight = 75 kg

Bill's labs reveal:

- Na 140 mmol/L
- K 4.5 mmol/L
- Cl 96 mmol/L
- Bicarbonate 23 mmol/L
- SCr 100 umol/L
- BUN 10 mmol/L
- A_1c 7%

How would *you* manage Bill's BP?

Other antihypertensives (*i.e.*, alpha blockers, central alpha-2 agonists, and arterial vasodilators) may be considered as third- and fourth-line agents, to be used as add-on therapy to reach target BP.

Q *How can patient adherence be improved?*

A
1. Involve patients in decision making and educate them on the difference between what their BP reading is and what the target BP is.
2. Educate patients on the *benefits* and side-effects of medications.
3. Teach patients that combination therapy is often required.
4. Simplify medication regimens.
5. Encourage greater patient responsibility in monitoring their own BP and adjusting medications.

Patients with diabetes are at increased cardiovascular risk. BP control, in addition to other measures of vascular protection, is necessary to reduce this increased risk. Achieving a BP target of < 130/80 mmHg should be a goal for all patients with diabetes, and this usually requires the use of multiple antihypertensive agents. *PCard*

Take-home message

- The target BP for patients with diabetes is < 130/80 mmHg.
- The majority of patients with diabetes should be on an ACE inhibitor for vascular protection.
- Multiple antihypertensive agents are usually required to achieve target BP.
- Choice of add-on therapy will depend on patient comorbidities, patient tolerance, allergies and mechanism of action of the antihypertensive agents.

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