

## A-B-C in Diabetes

Cardiovascular (CV) disease is an important cause of morbidity and mortality in persons with diabetes mellitus (DM). One study found that the risk of myocardial infarction (MI) and cardiac death in patients with type 2 DM and no history of MI is the same as patients without DM who have had a prior MI (*NEJM* 1998; 339:229-234). Other studies have reported smaller effects, but the message remains the same: patients with DM are at high risk of cardiovascular events. How can their long-term outcomes be improved? Research has shown that a multi-pronged management strategy (*the ABCs*) is central in managing vascular risk factors in DM.



**A**ngiotension converting enzyme inhibitors (ACEI) are medications that can provide benefits to persons with DM on several levels:

### 1 Cardiovascular disease

Research supports the use of ACEIs to reduce cardiovascular events in persons with DM and a vascular risk factor, hypertension or stable coronary artery disease, even without evidence of heart failure.

**Evidence:** The HOPE Study (*Lancet* 2000; 355:253-259) looked at the use of an ACEI in patients who were at high risk for cardiovascular events (had at least one CV risk factor), but did not have either left ventricular dysfunction or heart failure. In the large subset of patients with DM, the use of an ACEI led to significant reductions in death, MI or stroke. Similar findings were reported in the LIFE trial (*Lancet* 2002; 359:995-1003) which studied angiotension receptor blockers (ARBs) in patients with DM and hypertension. The EUROPA trial looked at the effects of an ACEI plus optimal therapy on preventing cardiac events in patients with stable

### Clinical options to manage common adverse reactions to ACE inhibitor use

Adverse reactions	Clinical options
✓ Angioedema	▶ Stop the drug.
✓ Cough	▶ Consider: 1) Stopping the drug. 2) Continuing if cough tolerable. 3) Switching to ARB.
✓ Elevated creatinine	<ul style="list-style-type: none"> <li>▶ If the creatinine is elevated but &lt;250 µmol/L, a trial of an ACEI is appropriate.               <ul style="list-style-type: none"> <li>• Start low and go slow (1/3 to 1/2 of usual dose).</li> <li>• Check creatinine and electrolytes two weeks after start, and monthly while increasing the dose.</li> <li>• Check creatinine and electrolytes every three months thereafter.</li> <li>• If creatinine rises, treatment may still be beneficial. If the rise is &lt;15% and not progressive, the ACEI can still be continued.</li> <li>• Consult a specialist as needed.</li> </ul> </li> <li>▶ If the creatinine is &gt; 250 µmol/L, ACEI may still be beneficial, but consider consultation with a specialist.</li> </ul>
✓ Elevated potassium	<ul style="list-style-type: none"> <li>▶ Check other sources (salt substitutes and potassium sparing diuretics, such as spironolactone).</li> <li>▶ In patients with hypertension, concomitant treatment with a thiazide diuretic will reduce both BP and potassium. (Thiazide diuretics are not effective with a serum creatinine &gt; 200 µmol/L.)</li> </ul>

coronary artery disease and no heart failure (*Lancet* 2003; 362:782-788). Analysis of the subgroup of patients with DM revealed that the number needed to treat (NNT) to prevent one CV death or non-fatal MI was just 27 patients over four years.

### 2 Renal disease

Kidney disease is a major complication in DM. Thirty percent of patients with type 2 DM will have evidence of kidney disease within four years of diagnosis. Research supports the use of ACEI to prevent progression of nephropathy.

**Evidence:** ACEI use in patients with type 1 DM and microalbuminuria (the earliest warning sign of diabetic nephropathy) has been shown to slow the progression of proteinuria and creatinine rise in several large clinical trials (*NEJM* 1993; 329:1456-1462). In type 2 DM, ACEIs and ARBs have been shown to decrease albuminuria and prevent worsening of nephropathy (*Ann Int Med* 1993; 118:577-581; *NEJM* 2001; 345:870-878).

**Using ACEI:** Three common adverse reactions to ACEIs are angioedema, cough, and elevated creatinine/potassium (see box above). Declining renal function is part of the long term disease process in DM. Finding the balance is sometimes difficult in those who already have some renal impairment but who can still benefit from ACEIs.

### Just to complicate matters...

The ALLHAT trial (*JAMA* 2002; 288:2981-2997) demonstrated that diuretics were as good or even better than ACEIs and calcium channel blockers in preventing CV events, even in the subgroup with DM. This result muddies the waters less than you might think, because most patients with DM will require at least two antihypertensive agents to reach the benchmark BP of 130/80 (see section on **Blood Pressure Reduction**). The combination of a diuretic plus an ACEI is attractive, because diuretics are potent, effective and inexpensive, and ACEIs offer the additional benefits of renal protection.

### Blood pressure reduction

has been targeted even lower in your patients with both DM and hypertension. Aim for a blood pressure (BP) less than 130/80 mm Hg.

**Evidence:** A series of large, long-term trials in Great Britain (the UKPDS trials) tested treatments used to prevent complications and mortality in persons with type 2 DM. One of the unexpected findings was that controlling blood pressure produced greater benefits than controlling blood glucose in terms of preventing the vascular complications of diabetes (UKPDS 38 in *BMJ* 1998; 317:703-713). In the HOT