

# ACEI and ARB Combination: A Promising Solution

Diabetes is one of the most significant health-care problems in Canada, and is associated with devastating microvascular complications. Angiotensin II is a significant contributor to the complications of diabetes, but its adverse effects can be reduced by ACEIs and ARBs—or a combination of the two.

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## Daulton's Diabetes



Daulton, 58, visits his family physician for a checkup. Ten years ago, he was identified as having hypertension and, five years ago, Type 2 diabetes.

Daulton's blood pressure (BP) is 150/90 mmHg, and his blood work is as follows:

- A1c: 8.4%
- Total cholesterol: 5.4 mmol/L
  - Low-density lipoprotein: 3.9 mmol/L
  - High-density lipoprotein: 0.9 mmol/L
- Triglycerides: 3.5 mmol/L
- Creatinine: 90 µmol/L
- Blood glucose: 10.0 mmol/L

## Cardiorenal disease in diabetes

Diabetes is one of the most significant health-care problems in Canada; the number of people with diabetes has risen by as much as one-third in five years. Over 6% of Canadians have been identified as having diabetes and, for every person in Canada with diabetes, there is likely another individual unaware of their condition.

Diabetes is associated with devastating microvascular complications, such as retinopathy and nephropathy, the cause of kidney failure in many diabetic patients. There is also a strong association between diabetes and cardiovascular disease.

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## Angiotensin II

Angiotensin II is a significant contributor to the complications of diabetes by:

- “tensing the angios,” contributing to hypertension,
- contributing to ventricular remodeling and the development of heart failure following myocardial infarction and
- accelerating mesangial expansion, contributing to the loss of kidney function in diabetic nephropathy.

Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) reduce the adverse effects of angiotensin II. ACEIs block the activation of angiotensin and increase levels of the vasodilator bradykinin. ARBs block the binding of angiotensin II to its receptor, even when it is activated by non-ACE pathways.

Clinical trials have shown that drugs that interfere with angiotensin II lower blood pressure, reduce progression of nephropathy, decrease cardiovascular risk and improve survival in people with diabetes. As the mechanisms of action of these drugs differ, this raises the possibility of differential clinical effects, as well as potential advantages to combination ACEI/ARB therapy.

### *Cardiorenal protection*

In 2003, the Canadian Diabetes Association (CDA) revised their guidelines for diabetes care,<sup>1</sup> which outline a comprehensive three-step approach to cardiorenal protection and highlight the role of angiotensin system drugs within this strategy (Table 1).

Step one states that vascular protection manoeuvres should be considered in all people with diabetes at high cardiovascular risk. ACEIs are included as a vascular protection manoeuvre, based on the results of trials, such as micro-HOPE<sup>2</sup> and EUROPA<sup>3</sup> (in micro-HOPE, cardiovascular event rates were reduced and survival improved in people with diabetes, regardless of whether they had hypertension, previous cardiovascular disease or nephropathy).

Some controversy remains about the ability of ARBs to reduce myocardial infarction rates in certain populations.<sup>4</sup> Whether ARBs or ACEI/ARB combination therapy should be used for general vascular protection is now under investigation.

The second step involves aggressive control of hypertension, with a target blood pressure of 130/80 mmHg (Table 1). Both ACEIs and ARBs lower blood pressure and improve survival in people with hypertension and diabetes.

#### FAQ

##### **Can an ACEI and an ARB be combined?**

These drugs can be combined safely, and this combination has been shown to be advantageous in heart failure and nephropathy. Be mindful of hyperkalemia and rising creatinine with this combination.

#### FAQ

##### **Why recommend an ACEI for vascular protection in people with diabetes who do not have high blood pressure?**

Many of the adverse effects of angiotensin II are not related to blood pressure and ACEIs have been shown to reduce cardiorenal risk in people with diabetes, even if they do not have hypertension.

#### FAQ

##### **What if a patient develops a cough on an ACEI?**

Be sure that the cough is related to the ACEI (*i.e.*, distinctive, bothersome, persistent, non-productive cough starting soon after ACEI initiation). Consider a lower dose of the ACEI or conversion to an ARB.

Combining an ACEI and an ARB lowers blood pressure more than either drug alone, but whether this approach is superior to other antihypertensive combinations is unclear.

The third step is control of nephropathy in those with kidney disease (Table 1). ACEIs reduce the development of nephropathy and both ACEIs and ARBs reduce progression of nephropathy and the likelihood of requiring dialysis. An ACEI/ARB combination reduces proteinuria more than either agent alone and is superior in preventing end-stage renal disease in non-diabetic nephropathy.<sup>5,6</sup>

### *Precautions*

ACEIs and ARBs can cause hyperkalemia or an elevated serum creatinine; bloodwork should be performed to check these parameters within two weeks of their initiation or titration. Hyperkalemia is usually mild and manageable with a

### FAQ

#### **What should be done when the potassium rises after starting an ACEI or an ARB?**

Mild hyperkalemia can typically be managed by decreasing potassium intake or increasing urinary potassium excretion. A low potassium diet can be facilitated by a dietician or by reminder sheets (try an Internet search for low-potassium diet information).

## Protecting Daulton

### Step 1: Vascular protection

Daulton should receive lifestyle advice regarding a healthy diet and regular exercise (at least 30 minutes, 4 times per week). Acetylsalicylic acid and angiotensin-converting enzyme inhibitor (ACEI) therapy should be considered, as well as interventions to improve lipids and glycemia.

### Step 2: Hypertension control

Daulton's BP is above the 130/80 mmHg target and the ACEI is not likely to lower his BP to the target. A thiazide-type diuretic (*e.g.*, chlorthalidone, 25 mg, daily) is an excellent addition for BP control and may reduce any tendency towards hyperkalemia. Most people with diabetes require three or more

antihypertensives to reach their target BP, so it is likely that additional medications will be required.

### Step 3: Control of nephropathy

If Daulton's BP or urinary protein level do not reach their target with the ACEI/diuretic combination, addition of an angiotensin-blocking receptor (ARB) or a non-dihydropyridine calcium channel blocker could be considered.

### Precautions

Serial monitoring of serum potassium and creatinine are needed after starting an ACEI or ARB. One should be especially mindful of potassium when ACEI/ARB therapies are combined.

Table 1

### The CDA Cardiorenal Protection Strategy

#### Vascular Protection

- Lifestyle changes—diet and exercise
- Two drugs—ASA and ACEI
- Jobs for patients and clinicians: Control blood sugar, cholesterol and BP

#### Hypertension Control

- Target and threshold BP of 130/80 mmHg
- Recommended antihypertensives in diabetes (in order of preference):
  - ACEI
  - ARB
  - Cardioselective beta-blocker
  - Thiazide-like diuretic
  - Long-acting calcium channel blocker

#### Control of Nephropathy

##### First line

- Type 1 DM—ACEI
- Type 2 DM—GFR  $\geq$  60 mL/min ACEI or ARB; GFR < 60 mL/min ARB

##### Second line

- ACEI/ARB combination or
- Non-DHP calcium channel blocker (diltiazem or verapamil)


CDA: Canadian Diabetes Association  
 ACEI: Angiotensin-converting enzyme inhibitor  
 ARB: Angiotensin II receptor blocker  
 GFR: Glomerular filtration rate

ASA: Acetylsalicylic acid  
 BP: Blood pressure  
 DM: Diabetes mellitus  
 DHP: Dihydropyridine

low-potassium diet and diuretics; however, severe hyperkalemia can limit the use of these drugs.

Creatinine can rise up to 30% from baseline, representing changes in intrarenal hemodynamics rather than kidney damage. Typically, there is no need to hold these medications when such a rise in creatinine is seen. There is also a low risk of allergic reactions with these drugs.

## Conclusions

Drugs that interfere with the effects of angiotensin II play prominent roles in the cardiorenal protection strategy for people with diabetes. The CDA 2003 guidelines outline how these drugs can be used as part of this strategy. Exciting research is underway that will further our understanding of the use of these drugs in people with diabetes. 

#### References

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