# Solo or Duet?: ACEs and ARBs & Diabetes

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Type 2 diabetes affects over 6% of the Canadian population and the prevalence continues to rise. Diabetes is associated with a variety of potentially devastating microvascular complications, such as neuropathy and blindness.

Hypertension is more than twice as common in people with diabetes as are macrovascular events such as heart attack and stroke. Significant kidney damage is more than 10 times as common in people with diabetes. All of these complications can reduce the quality and the length of an individual's life.

The Canadian Diabetes Association (CDA) clinical practice guidelines recommend a three-step approach to reducing cardiovascular and renal complications in people with diabetes. They recommend:

1) Starting with a multifactorial vascular protection strategy
2) Moving on to aggressive control of BP
3) Ending with maneuvers that are specifically renoprotective.[1]

## Combining ACEs and ARBs

The renin-angiotensin system is recognized as an important player in the development of the complications of diabetes, as angiotensin II can induce injury through both BP dependent and independent mechanisms. Angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) have been demonstrated to effectively lower BP and prevent cardiovascular and renal events in people with diabetes and play a prominent role in the CDA cardiorenal protection strategy.

Recent research has examined whether combining an ACE inhibitor and an ARB might be more effective in people with diabetes than if they were to use only one of the agents. ACE inhibitors block ACE and prevent the conversion of angiotensin-I to its active and potentially harmful form of angiotensin II (Figure 1). ACE inhibitors also reduce the breakdown of bradykinin, a potent coronary vasodilator that may have cardioprotective effects.

ARBs block the adverse effects of angiotensin II at the receptor level. This is important, as there are several metabolic pathways other than ACE that can activate angiotensin II, and ARBs will block the effect of angiotensin II regardless of how it was activated.

## The Benefits of combining ACEs and ARBs

These are the following benefits of combining ACEs and ARBS:

1) Adding an ACE inhibitor to an ARB could provide a more effective angiotensin II blockade, as well, it has potentially beneficial effects of higher bradykinin levels.
2) Adding an ARB to an ACE inhibitor could lead to a more effective blockade of angiotensin II by blocking its effects

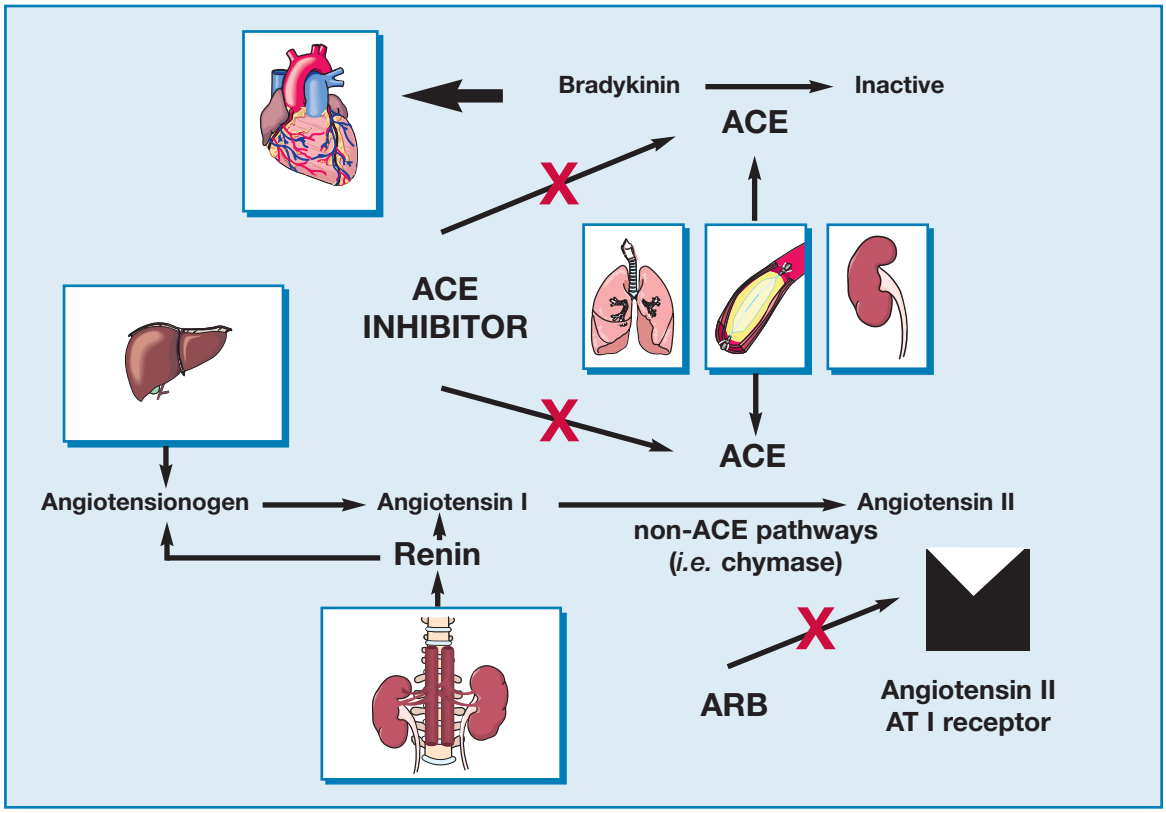


Figure 1. ACE inhibitors and ARBs and the renin-angiotensin system.

regardless of whether activation occured by an ACE or non-ACE pathway.

These potential synergies provide a rationale for combining these agents and now clinical trials are reporting about the experience with this combination.

Control of nephropathy with ACE inhibitor and ARB therapy has been studied in both diabetic and non-diabetic nephropathy. In people with diabetes, proteinuria is reduced further with combination therapy than with either agent alone.[2] In non-diabetic nephropathy, this combination is more effective at preventing renal failure.[3]

Combination ACE inhibitor and ARB therapy also appears to lower BP more than either agent alone,[4] although it is unclear if this combination is more effective than other potential antihypertensive combinations.

## *Look out for the the ONTARGET clinical trial*

Although data in patients with heart failure suggests additional cardiovascular protection from the combination of ACEs and ARBs,[5] definitive evidence of general vascular protection is currently lacking. However, the ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) is expected to report in 2007. This trial is testing the cardioprotective effects of angiotensin system medications, with patients randomized to an ACE inhibitor, an ARB or an ACE inhibitor and ARB combination.

As there are approximately 30,000 people participating in ONTARGET, including many with diabetes, the results will provide guidance as to the value of applying ACE inhibitor and ARB therapy, broadly, in people with diabetes.

A number of cautions apply to the use of

Table 1

**Precautions when using ACEIs and ARBs**

| | How to Monitor | Response |
|---|---|---|
| **Hyperkalemia** | Bloodwork within one to two weeks of start/ titration | • Low potassium diet<br>• Diuretics (first thiazides,then furosemide)<br>• Hold ACE inhibitor/ARB (if severe or refractory) |
| **Rising creatinine** | Bloodwork within one to two weeks of start/ titration | • Rule out volume contraction hold only if rise > 30% above baseline<br>• Consider workup/ referral for renovascular disease |
| **Cough** | Applies only to ACE inhibitor | • Hold to see if cough resolves<br>• Consider rechallenge<br>• Rule out other causes of cough (especially congestive heart failure) |
| **Angioedema** | Monitor for clinical signs/ symptoms | • Discontinue ACE inhibitor/ ARB<br>• Do not rechallenge with angiotensin system medication |

ACEI plus ARB combination therapy. Potassium and creatinine levels should be checked between one and two weeks after initiation or titration of either mono or combination therapy with an ACE inhibitor or an ARB. Table 1 lists some conditions that should be monitored for people receiving ACE inhibitor and ARB combination therapy.

## *Initial studies of ACE inhibitor and ARB combination therapy*

Angiotensin II is an impotant promoter of the complications of diabetes and the effective angiotensin system blockade appears to reduce organ damage in diabetes through BP dependent and independent mechanisms. Initial studies of ACE inhibitor and ARB combination therapy have shown encouraging results, especially in the area of nephropathy. The results of upcoming large cardiovascular trials will help further define the populations that could benefit from this approach.

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