



“An Ace in the Hole”

*From HOPE to DREAM with Less Diabetes at the
End of the Rainbow!*

Evan David Rosen, M.D., Ph.D.

Assistant Professor of Medicine, Harvard Medical School

ACE inhibitors, are used to reduce blood pressure in patients with hypertension. ACE inhibitors are also known to reduce the likelihood of developing diabetic kidney disease, and it is for this reason that many physicians (myself included) use ACE inhibitors liberally in people with both diabetes and high blood pressure.

A study has been published suggesting that ACE inhibitors may be able to prevent type 2 diabetes in patients at risk for that disease.

Here's the backstory:

ACE inhibitors have effects on the heart, blood vessels, and kidneys that led some investigators to believe that they might prevent heart attacks and strokes. To test this, the Heart Outcomes Prevention Evaluation, or HOPE, trial was devised. This trial proved that 1) ACE inhibitors do, in fact, prevent many of the serious complications of vascular disease, and 2) doctors will unabashedly contort trial names in order to squeeze out a clever acronym. The specific ACE inhibitor used in the HOPE trial was ramipril, which is sold in the U.S. under the name Altace™. There were lots of interesting things about the HOPE trial, but one of the more curious observations was that fewer patients taking ramipril went on to develop type 2 diabetes than did people taking placebo. The new study is really a re-analysis of those data done to take a closer look at this phenomenon.

This re-appraisal of the HOPE data shows that about 3.6 % of patients receiving a daily dose of 10 mg ramipril developed diabetes, while 5.4% of those taking a placebo were given such a diagnosis, over a four year period. This difference was very significant, and appeared no matter how the investigators defined diabetes. The numbers may seem small to you, but bear in mind that diabetes is a very common disorder. A difference of even a few percentage points translates to thousands of cases of diabetes.

All this begs the question of why ACE inhibitors have this effect on diabetes at all. There are actually quite a few possible (indeed, plausible) explanations, although nothing in particular has been proven yet. First, ACE inhibitors may help the insulin-secreting beta cells of the pancreas by increasing their blood flow, or by slightly raising potassium levels, which has been shown to increase the amount of insulin release. ACE inhibitors also block the degradation of certain hormones, which may have beneficial effects on sugar uptake by the muscles. Additionally, ACE inhibitors prevent the actions of still other hormones

that can lead to poisoning of the insulin receptor in fat, liver, and muscle.

So, what's the catch?

Basically, there really isn't one, as long as these results replicate in a new large trial designed to specifically address this issue (remember, the HOPE trial was not actually designed to look at diabetes, and statistically, that calls the results into some question). ACE inhibitors are relatively safe and cheap, though there are occasional side effects that prevent some people from using them. For example, some people show reduced kidney function on an ACE inhibitor, or elevated potassium levels that if unnoticed and untreated can be quite serious. A simple blood test drawn a week or so after starting the drug usually suffices to warn of this, though. Additionally, a certain percentage of people will develop a benign yet annoying cough while taking ACE inhibitors; stopping the pills leads to rapid resolution of this problem as well.

Because of the huge potential payoff if it turns out that ACE inhibitors really do prevent the onset of type 2 diabetes, these same investigators are working on a brand new clinical trial designed specifically to answer the question definitively. This trial will also involve the thiazolidinedione drug rosiglitazone, and is called the Diabetes Reduction Assessment with ramipril and rosiglitazone Medication, or DREAM. From HOPE to DREAM we go then, keeping our fingers crossed for the possibility of less diabetes at the end of the rainbow.

Reference

Salim Yusuf, DPhil, FRCPC; Hertzell Gerstein, FRCP; Byron Hoogwerf, MD; Janice Pogue, MSc; Jackie Bosch, MSc; Bruce H. R. Wolffenbuttel, MD; Bernard Zinman, FRCP; for the HOPE Study Investigators. Ramipril and the Development of Diabetes. *Journal of the American Medical Association* 2001; 286: 1882-1885.