

## Providing HOPE in the Campaign Against Cardiovascular Morbidity and Mortality



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**H**ope describes precisely what Dr. Salim Yusuf, McMaster researcher, cardiologist and chair of the Heart Outcomes Prevention Evaluation (HOPE) study has uncovered for populations at high risk for cardiovascular death.



*Dr. Salim Yusuf, McMaster researcher, cardiologist and chair of the Heart Outcomes Prevention Evaluation (HOPE) study*

### THE HOPE STUDY

Studies demonstrate that Angiotensin Converting Enzyme Inhibitors (ACE-Inhibitors) reduce morbidity and mortality in patients with low ejection fraction with and without heart failure (Yusuf et al., 1992). However, the impact of ACE-Inhibitors on preventing heart failure in patients without pre-existing heart failure, low ejection fraction, or hypertension remains unexplored. The primary purpose of the HOPE study was to evaluate the usefulness of Ramipril, an ACE-Inhibitor, in the reduction of cardiovascular events in high risk patients without pre-existing heart failure or low ejection fraction.

The outcomes evaluated by this multi-center randomized controlled trial are a composite of myocardial infarction (heart attack), stroke and cardiovascular death. The HOPE study was conducted over six years and included 9297 high risk patients (55 years of age or



(<http://www.med-ars.it/galleries/heart1.htm>)



older) with evidence of vascular disease or diabetes, from nineteen countries across North America, South America and Europe. This study has the distinction of being one of the largest clinical trials to address cardiovascular disease prevention for high risk patients, such as diabetics.

The HOPE study demonstrates the effectiveness of ACE-Inhibitor regimens in the prevention of cardiovascular events in high risk patients. A total of 651 patients randomized to treatment with Ramipril (14%) reached a primary outcome in comparison with 862 in the placebo group (17.8%). Furthermore, treatment with Ramipril reduced the rates of cardiovascular death, myocardial infarction, stroke, cardiac arrest, heart failure and complications related to diabetes (HOPE Investigators, 2000b). The benefit of Ramipril was at least as great as that observed with other proven secondary prevention measures, such as beta-blockers (Yusuf et al., 1985), aspirin (Antiplatelet Trialists' Collaboration, 1994) and lipid-lowering agents (Law, 1998).

### ANGIOTENSIN CONVERTING ENZYME (ACE) INHIBITORS

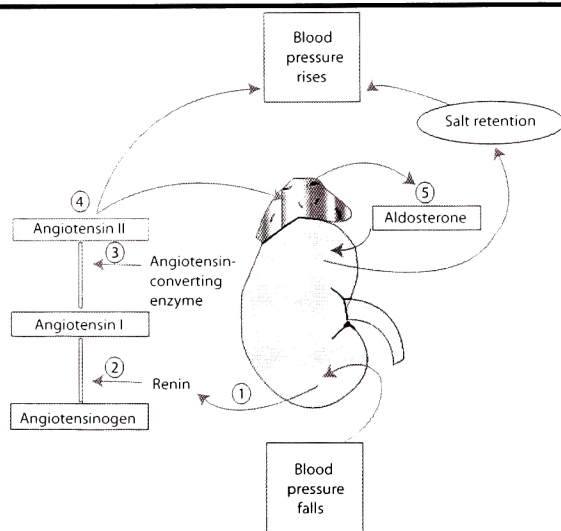
ACE-Inhibitors are a class of drugs originally developed to lower the blood pressure of hypertensive patients. Their function is to interfere with one of the body's blood pressure and blood volume regulatory pathways, the renin-angiotensin system. The key to understanding the activity of ACE-Inhibitors is to understand the physiology underlying the renin-angiotensin system.

#### Renin-Angiotensin System

The renin-angiotensin system is a series of reactions designed to regulate blood pressure and extracellular volume. It consists of the following steps:

- 1) When blood pressure drops, the kidneys release the enzyme renin into the bloodstream
- 2) Renin splits angiotensinogen, a large protein that circulates in the blood stream, into pieces. One piece is angiotensin I.
- 3) Angiotensin I, which is relatively inactive, is split into pieces by angiotensin-converting enzyme (ACE). One piece is angiotensin II, which is very active.
- 4) Angiotensin II, a hormone, causes the muscular walls of small arteries to constrict, increasing blood pressure. Angiotensin II also triggers the release of the hormone aldosterone from the adrenal glands which are located above the kidneys.

5) Aldosterone causes the kidneys to retain salt (sodium) and excrete potassium. The sodium increases plasma oncotic pressure. This causes water to be retained, thus increasing blood volume and consequentially blood pressure.



**Figure 1:** The Renin-Angiotensin System ([www.merck.com](http://www.merck.com))

ACE-Inhibitors interfere with the cleavage of the relatively inactive angiotensin I into the active hormone angiotensin II by ACE. In the absence of angiotensin II, the renin-angiotensin pathway is unable to mediate any corresponding increases in blood pressure or alterations to the vasculature.

### CONUNDRUM OF THE HOPE STUDY

The beneficial treatment effect observed in the HOPE study was much greater than could be accounted for by the small reduction in blood pressure induced by Ramipril (3/2 mm Hg). The investigators hypothesized that antagonizing alternative actions of the renin-angiotensin system may account for the treatment effect. They have focused upon antagonizing the direct effects of angiotensin II on vasoconstriction, rupture of plaques and thickening of blood vessels, all of which contribute to cardiovascular morbidity (Lonn et al., 1994).

### ADDITIONAL HOPE FOR DIABETICS

Individuals with diabetes mellitus are at high risk of cardiovascular disease. Epidemiological studies have shown that the risk of cardiovascular mortality is two to three times greater in men with diabetes (Stalmer et al., 1993) and three to five times greater in women with diabetes (Manson et al., 1991) than in persons without diabetes. Although the HOPE study was not restricted to patients with diabetes, it was an inclusion risk factor for the trial

and 3577 of the participants were diabetic. After investigating separately the data from those patients with diabetes, investigators found that Ramipril significantly lowered the risk of major cardiovascular outcomes by 25–30% in a range of high-risk middle-aged and elderly people with diabetes mellitus (HOPE Investigators, 2000a).

A more effective approach to preventing these complications would be to prevent the development of diabetes. Many recent trials suggest that lifestyle changes lead to a reduced risk of diabetes (Pan et al., 1997); however the long-term adherence to these regimens remains questionable.

The HOPE investigators subsequently analyzed the effects of Ramipril on the incidence of new cases of diabetes in their study population. They found that treatment with Ramipril decreased the risk of developing diabetes by 33% (Yusuf et al., 2001b). While these findings are promising, they require further confirmation. They will be studied in the upcoming DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) study.

### COST EFFECTIVENESS OF HOPE

A treatment regimen should be cost effective, in addition to improving clinical outcomes. In the United States and Canada, the use of Ramipril based on the approach of the HOPE trial is a realistic strategy. It not only improves clinical outcomes, such as cardiovascular death, myocardial infarction, and stroke, but also greater than 90% of the cases fall into a cost-saving or cost-neutral situation (Lamy et al., 2003).

### CLINICAL IMPLICATIONS OF THE HOPE STUDY

The results of the HOPE study have made available yet another powerful tool in the battle against cardiovascular events in high risk patients. Subsequent to the trial, the use of Ramipril in a clinical setting experienced a substantial increase. Yusuf has attributed this increase to its ease of use, proven cost effectiveness and the very clear effect in reducing myocardial infarction, stroke and death, in addition to heart failure and diabetes (Taubes, 2002).

In regards to the larger goal of eradicating the threat of cardiovascular disease, Yusuf believes that “we now have the knowledge to do it, but we have to implement it. By that I mean getting the smokers to stop smoking—right there you can reduce the risk of future heart attack by 40–50%. Getting people to lose weight. If they lose four to five kilograms, that can have a big effect...Targeting obesity will be a big issue for the future but we’re not there yet” (Taubes, 2002). **M**