Effect of Ramipril in Reducing Sudden Deaths and Nonfatal Cardiac Arrests in High-Risk Individuals Without Heart Failure or Left Ventricular Dysfunction

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**Background**—ACE inhibitor therapy reduces the risk of cardiovascular death, myocardial infarction, stroke, hospitalization for heart failure, and need for revascularization in high-risk patients with clinical heart failure, overt left ventricular systolic dysfunction, or vascular disease. In patients with clinical heart failure or overt left ventricular systolic dysfunction, ACE inhibitor therapy also reduces the risk of sudden or arrhythmia-related cardiac death. The objective of this study was to assess the effect of the ACE inhibitor ramipril on sudden unexpected death or resuscitated cardiac arrest among the 9297 individuals without clinical heart failure or overt left ventricular dysfunction enrolled in the Heart Outcomes Prevention Evaluation (HOPE) trial.

**Methods and Results**—During the median follow-up of 4.5 years, the composite outcome of unexpected death, documented arrhythmic death, or resuscitated cardiac arrest was reduced by 21% in patients randomized to ramipril therapy compared with those randomized to placebo. There were 155 (3.3%) composite outcome events in patients randomized to ramipril therapy compared with 195 (4.2%) such events in patients randomized to placebo (RR 0.79, 95% CI 0.64 to 0.98, \(P=0.028\)). There were trends toward reductions in fatal primary outcome events (unexpected death or documented arrhythmic death; RR 0.81, 95% CI 0.64 to 1.02, \(P=0.072\)) and in nonfatal primary outcome events (resuscitated cardiac arrest; RR 0.65, 95% CI 0.38 to 1.13, \(P=0.127\)) in the ramipril treatment group.

**Conclusions**—Ramipril reduces the risk of fatal and nonfatal serious arrhythmic events in high-risk patients without clinical heart failure or overt left ventricular systolic dysfunction. (**Circulation.** 2004;110:1413-1417.)

**Key Words:** angiotensin • arrhythmia • death, sudden • heart arrest • resuscitation

Activation of the renin-angiotensin-aldosterone system leads to elevated levels of angiotensin II, which mediates an increased risk of cardiovascular disease events. Conversely, ACE inhibitors, which reduce the production of angiotensin II, reduce the risk of cardiovascular disease events in patients with heart failure, left ventricular dysfunction, or coronary artery disease and in other high-risk individuals with diabetes and/or vascular disease without heart failure or left ventricular dysfunction. In these patient populations, the benefits of ACE inhibitor therapy include reductions in the risk of cardiovascular death, myocardial infarction, stroke, hospitalization for heart failure, and need for revascularization. Sudden or unexpected cardiac deaths constitute a substantial proportion of deaths due to cardiovascular causes. An overview of early trials of ACE inhibitors, involving patients with congestive heart failure, reported that ACE inhibitor therapy principally reduced deaths due to progressive heart failure. Nevertheless, there was a trend toward a reduction in sudden death. Subsequent trials have also shown trends toward fewer sudden or arrhythmia-related deaths in patients assigned to ACE inhibitors compared with controls in patients with heart failure or left ventricular dysfunction. A meta-analysis of randomized trials in patients after myocardial infarction and with heart failure or left ventricular dysfunction showed that ACE inhibitor therapy significantly reduced cardiovascular mortality and sudden cardiac death. This consistency of observations across a range of studies strongly suggests the likelihood that ACE inhibitor therapy reduces the risk of sudden death in patients with left ventricular dysfunction or heart failure. Whether ACE inhibitor therapy would lead to a reduction in sudden cardiac death in other high-risk individuals without heart failure or left ventricular dysfunction is not known. Furthermore, little is known of the impact of ACE inhibitor therapy on preventing nonfatal cardiac arrest in these patients. The present report

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examines the effect of ACE inhibitor therapy with ramipril on arrhythmia-related or sudden cardiac death and on nonfatal cardiac arrest in the Heart Outcomes Prevention Evaluation (HOPE) study, which specifically excluded patients with known heart failure or left ventricular dysfunction.

Methods

The HOPE study was a large, simple, double-blind, randomized trial with a 2 × 2 factorial design in which 9297 high-risk men and women were randomly assigned to active ramipril therapy (up to 10 mg/d) or matching placebo and to active vitamin E therapy (400 IU/d) or matching placebo. The details of the HOPE trial design and main outcomes have been published.\textsuperscript{10,12}

Study Population

Participants in this study were recruited over a period of 18 months from centers in Canada, the United States, 14 western European countries, Argentina, Brazil, and Mexico. The average follow-up was 4.5 years. To be eligible, participants had to be ≥55 years old, with documented ischemic heart disease, nondebilitating stroke, peripheral arterial disease, or diabetes with at least 1 of the following risk factors: current cigarette smoking, blood cholesterol ≥5.2 mmol/L, HDL cholesterol <0.9 mmol/L, systolic blood pressure >160 mm Hg, diastolic blood pressure >90 mm Hg, or microalbuminuria. Main exclusion criteria included current use of or hypersensitivity to an ACE inhibitor or vitamin E; known left ventricular ejection fraction <0.40; congestive heart failure; acute myocardial infarction, unstable angina, or multivessel percutaneous coronary intervention occurring <1 month before enrollment; or multivessel CABG surgery <4 years before entry. Also excluded were patients with renal dysfunction, uncontrolled hypertension, or other major illness that might affect study outcomes.

Interventions

After a 3-week run-in phase of screening for tolerance and compliance, eligible participants were randomly assigned to receive ramipril or matching placebo, 2.5 mg daily for 1 week, 5 mg daily for 3 weeks, and then 10 mg daily for the duration of the trial, and to vitamin 400 IU/d or matching placebo. After random assignment, patients were followed up at 1 month and 6 months and then every 6 months until completion of the trial.\textsuperscript{12}

Study Outcomes

Criteria for all study outcomes were defined in advance. An Events Adjudication Committee blinded to treatment assignment reviewed all main outcome reports, including all deaths, cardiovascular deaths, and cardiac arrests. Unexpected death was defined as death that occurred within 24 hours of the onset of symptoms without clinical or postmortem evidence of other identifiable causes, eg, acute myocardial infarction. For the purpose of the present study, sudden cardiac death was defined as the composite of unexpected deaths plus documented cardiac arrhythmic deaths. A documented cardiac arrhythmic death was defined as death preceded by a serious ventricular arrhythmia such as ventricular tachycardia without documented evidence of acute myocardial ischemia. Nonfatal cardiac arrest was defined as resuscitated cardiac arrest with survival to hospital admission. The primary outcome of the present study was the composite of sudden cardiac death and nonfatal cardiac arrest.

Statistical Analysis

Event frequencies are compared as relative risks (RRs) for the event in the ramipril group compared with the placebo group. RRs were estimated by the Cox regression model\textsuperscript{13} stratified according to random assignment to vitamin E or placebo to account for the factorial design. Survival curves were estimated by the Kaplan-Meier procedure.\textsuperscript{14}

Results

The mean age of the 9297 participants was 65.9 years, and 26.7% were women. Of these participants, 80.6% had a previous coronary event, 43.4% had peripheral artery disease, 10.8% had previous stroke or transient ischemic attack, 38.3% had diabetes mellitus, 46.5% had hypertension, and 65.8% had dyslipidemia. At entry into the HOPE trial, 76.3% were taking an antplatelet drug, 28.9% were taking lipid-lowering drugs, 39.5% were taking a β-blocker, 47.0% were taking a calcium channel blocker, and 15.1% were taking diuretics. Additional details of the patient baseline characteristics have been described elsewhere.\textsuperscript{10} No significant imbalances were noted between subjects assigned to ramipril and subjects assigned to placebo with respect to past history, baseline drug therapy, or other prognostic factors. Vital status was known in 99.8% of participants.\textsuperscript{10}

For vitamin E therapy, there were no significant differences in the primary outcome of myocardial infarction, stroke, and cardiovascular death or other end points between patients assigned to vitamin E and those assigned to placebo.\textsuperscript{15} The vitamin E arm will not be further considered in the present study.

Primary Outcome

The composite outcome of sudden death and nonfatal resuscitated cardiac arrest was significantly reduced by 21% in the patients randomized to ramipril therapy compared with those randomized to placebo. There were 155 (3.3%) primary outcome events in patients randomized to ramipril therapy and 195 (4.2%) in patients randomized to placebo (RR 0.79, 95% CI 0.64 to 0.98, P = 0.028; Figure 1).

There were 132 (2.8%) sudden deaths in patients randomized to ramipril therapy compared with 162 (3.5%) in patients randomized to placebo (RR 0.81, 95% CI 0.64 to 1.02, P = 0.072). Of these 294 sudden deaths, 182 (62% of total) were witnessed, and 87 (30% of total) occurred in the hospital. Sudden deaths were classified as unexpected deaths or cardiac arrhythmic deaths. Unexpected deaths occurred in 61 patients (1.3%) randomized to ramipril and 78 (1.7%) randomized to placebo (RR 0.78, 95% CI 0.56 to 1.09,
Documented cardiac arrhythmic death occurred in 71 patients (1.5%) randomized to ramipril therapy and 84 (1.8%) randomized to placebo (RR 0.84, 95% CI 0.61 to 1.15, \( P=0.271 \)). Information from autopsy findings was not available in many of the cases.

Cardiac arrests were reported in 37 patients (0.80%) randomized to ramipril and 58 (1.5%) assigned to placebo (RR 0.66, 95% CI 0.41 to 0.94, \( P=0.023 \)). Cardiac arrests with survival occurred in 23 patients (0.5%) randomized to ramipril therapy and in 33 (0.7%) randomized to placebo (RR 0.65, 95% CI 0.38 to 1.13, \( P=0.127 \)). The effects of ramipril on the primary outcome variable of sudden death and nonfatal resuscitated cardiac arrest were consistent across the important subgroups, as shown in Figure 2.

**Discussion**

The major new finding in this study is that long-term use of an ACE inhibitor is associated with a reduced risk of apparent sudden cardiac death or resuscitated cardiac arrest in patients at risk for atherosclerotic cardiovascular events but without overt left ventricular systolic dysfunction or heart failure. This finding is consistent with observations in other patient populations at higher risk of life-threatening arrhythmias.\(^2\,5\,6\,11\,16\,17\) A meta-analysis of the earlier trials of ACE inhibitors in patients with heart failure or left ventricular systolic dysfunction reported that although deaths due to progressive heart failure were reduced by a significant 31% (OR 0.69, 95% CI 0.58 to 0.83, \( P<0.001 \)), a nonsignificant 9% trend was noted with respect to the reduction in risk of sudden death (OR 0.91, 95% CI 0.73 to 1.12, \( P=0.37 \)).\(^2\) Although the SOLVD (Studies Of Left Ventricular Dysfunction) treatment trial observed only a 10% nonsignificant relative risk reduction in death classified as being due to arrhythmia (RR 0.90, 95% CI 0.83 to 1.31, \( P=0.21 \)),\(^7\) other trials have reported more impressive differences.\(^5\,6\,11\) In the Second Veterans Administration Cooperative Vasodilator–Heart Failure Trial (V-HeFT II) comparing enalapril therapy versus hydralazine-isosorbide dinitrate combination therapy in patients with symptomatic heart failure, sudden cardiac deaths, both with and without warning, were separately and significantly reduced with ACE inhibitor therapy by 42% (\( P=0.032 \)) and 35% (\( P=0.015 \)), respectively.\(^11\) The Trandolapril Cardiac Evaluation (TRACE) study evaluated the effects of ACE inhibitor therapy in the early postinfarction period in patients with left ventricular ejection fraction <35%. Trandolapril was associated with a significant 24% reduction in sudden death (RR 0.76, 95% CI 0.59 to 0.98, \( P=0.03 \)).\(^5\) Although reductions in the risk of sudden death were less obvious in the Fourth International Study of Infarct Survival (ISIS-4)\(^16\) and Cooperative New Scandinavian Enalapril Survival Study II (CONSENSUS II)\(^17\) post–myocardial infarction trials, a meta-analysis of randomized trials in patients after acute myocardial infarction and followed up for 6 or more weeks reported that ACE inhibitor therapy was associated with significant reductions in risk of cardiovascular death (OR 0.82, 95% CI 0.69 to 0.97, \( P<0.05 \)) and in risk of sudden cardiac death (OR 0.80, 95% CI 0.70 to 0.92, \( P<0.05 \)).\(^9\) The results of the present study indicate that ACE inhibitor therapy also reduces the risk of sudden death in patients at risk of atherosclerotic cardiovascular events who do not have clinical heart failure, overt left ventricular systolic dysfunction, or acute myocardial infarction.

The mechanisms by which ACE inhibitors reduce sudden cardiac death are not known. Nevertheless, ACE inhibitor therapy does provide a number of cardioprotective effects, including modulation of neurohormonal activation; restoration of the balance between oxygen supply and demand, thereby reducing ischemia; reduction in left ventricular mass; and other potentially beneficial structural cardiac and vascular effects.\(^1\) The net outcome of these effects of ACE inhibitor therapy would be expected to be a reduction in the probability of life-threatening ventricular tachyarrhythmias that are usually responsible for sudden death. Indeed, the ACE inhibitor cilazapril has been shown to reduce the incidence of serious ventricular arrhythmias and nonsustained ventricular tachycardia in patients with symptomatic heart failure.\(^18\)
By modulating the effects on neurohormonal activation, ACE inhibitor therapy can exert a potential indirect antiarrhythmic effect. These modulating effects have been well studied. Patients with congestive heart failure have elevated levels of angiotensin II, aldosterone, atrial natriuretic factor, norepinephrine, and adrenaline owing to activation of the neurohormonal system.\textsuperscript{19–21} Patients with left ventricular systolic dysfunction without overt heart failure have elevations of these neurohormones that are intermediate between those of normal individuals and patients with clinical heart failure.\textsuperscript{21,22} In CONSENSUS, elevated levels of these neurohormones were associated with increased probability of subsequent mortality.\textsuperscript{23} In the SOLVD treatment trial, patients receiving enalapril therapy tended to have a greater treatment-related decrease in plasma norepinephrine levels than those receiving placebo ($P=0.08$).\textsuperscript{24} This reduction in plasma norepinephrine levels after the introduction of enalapril therapy was highly statistically significant in patients with high baseline plasma norepinephrine levels ($P<0.01$).\textsuperscript{24} Enalapril also decreased levels of atrial natriuretic peptide regardless of baseline values.\textsuperscript{24} Similar effects of enalapril were also observed in CONSENSUS.\textsuperscript{23}

The adverse effects of chronic elevation of these neurohormones include vasoconstriction and increased myocardial oxygen demand, which could lead to myocardial ischemia and a propensity for ventricular tachyarrhythmias.\textsuperscript{1} In animal models of experimental acute myocardial infarction, ACE inhibitors have been shown to reduce ventricular arrhythmias.\textsuperscript{25–27} Restoration of the imbalance between myocardial oxygen supply and demand by ACE inhibitor therapy has the potential to reduce the risk of arrhythmia-related sudden cardiac death.\textsuperscript{1} In addition, chronic elevation of these neurohormone levels has been associated with an increase in cardiac ACE expression and formation of tissue angiotensin II, with subsequent myocardial hypertrophy and fibrosis, which interferes with appropriate cardiac remodeling and predisposes to life-threatening ventricular tachyarrhythmias.\textsuperscript{1} Reversal of these effects may also explain in part the reduction in sudden death after ACE inhibitor therapy even in the absence of clinical heart failure or overt left ventricular systolic dysfunction.

In populations in which the risk of sudden cardiac arrhythmic death is higher than that of other competing causes of deaths, such as heart failure, the benefits of ACE inhibitor therapy in reducing these sudden deaths may become more pronounced. Recently, the EUROPA trial (EUnopoean trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease)\textsuperscript{28} reported a reduction, although not statistically significant, in the risk of cardiac arrests with perindopril therapy (RR 0.54, 95% CI 0.20 to 1.47, $P=0.22$) in patients with established coronary artery disease and with many characteristics similar to the participants in HOPE. The consistent benefits in reducing sudden deaths by ACE inhibitor therapy documented in this and other trials appear real and may be of considerable importance in other populations at risk of arrhythmic deaths, such as survivors of the sudden cardiac death syndrome. The observation in the present study that the divergence of the curves occurred only after 2 years would tend to support the concept that the beneficial protec-
tive effects of ramipril were more likely due to effects in preventing ventricular remodeling and in reduction of myocardial ischemic events than to an immediate direct effect of the ACE inhibitor on reducing blood pressure.

**Study Limitations**

The definitions and ascertainment of sudden death and arrhythmic events are difficult in this and other trials and are not uniform among the trials. Furthermore, a sudden cardiac death is not always an arrhythmic death. Deaths that occur suddenly and unexpectedly in previously asymptomatic individuals can be due to fatal cardiac arrhythmia or to other causes, such as pulmonary embolism, cardiac rupture in the setting of an acute infarction, massive stroke, and rupture of an aortic aneurysm. In the present study, there was a requirement that patients who had unexpected sudden deaths should be asymptomatic outside of the 24 hours before the occurrence of the death. We have not used the other commonly used definition of death within 1 hour of symptoms because many of the deaths were not witnessed, and some patients subsequently died after initial successful resuscitation from cardiac arrest.

**Conclusions**

This analysis of the HOPE results indicates that ACE inhibitor therapy with ramipril is associated with a 21% reduction in the subsequent risk of sudden death in patients who are at risk of atherosclerotic cardiovascular events in the absence of clinical heart failure or overt left ventricular systolic dysfunction.

**Disclosure**

Dr Koon Teo has received grants and honoraria from Boehringer and Merck. Dr Salim Yusuf has received grants and honoraria from Aventis, AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, and Sanofi.

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