Reduction of Cardiovascular Risk by Regression of Electrocardiographic Markers of Left Ventricular Hypertrophy by the Angiotensin-Converting Enzyme Inhibitor Ramipril

James Mathew, MD, FCCP; Peter Sleight, MD, FRCP; Eva Lonn, MD, MSc; David Johnstone, MD; Janice Pogue, PhD; Qilong Yi, PhD; Jackie Bosch, MS; Bruce Sussex, MD, FRCPC; Jeffrey Probstfield, MD; Salim Yusuf, MBBS, DPhil, FRCP; for the Heart Outcomes Prevention Evaluation (HOPE) Investigators

Background—Electrocardiographic markers of left ventricular hypertrophy (LVH) predict poor prognosis. We determined whether the ACE inhibitor ramipril prevents the development and causes regression of ECG-LVH and whether these changes are associated with improved prognosis independent of blood pressure reduction.

Methods and Results—In the Heart Outcomes Prevention Evaluation (HOPE) study, patients at high risk were randomly assigned to ramipril or placebo and followed for 4.5 years. ECGs were recorded at baseline and at study end. We compared prevention/regression and development/persistence of ECG-LVH in the two groups and related these changes to outcomes. At baseline, 676 patients had LVH (321 in the ramipril group and 355 in the placebo group) and 7605 patients did not have LVH (3814 in the ramipril group and 3791 in the placebo group). By study end, 336 patients in the ramipril group (8.1%) compared with 406 in the placebo group (9.8%) had development/persistence of LVH; in contrast, 3799 patients in the ramipril group (91.9%) compared with 3740 in the placebo group (90.2%) had regression/prevention of LVH (P=0.007). The effect of ramipril on LVH was independent of blood pressure changes. Patients who had regression/prevention of LVH had a lower risk of the predefined primary outcome (cardiovascular death, myocardial infarction, or stroke) compared with those who had development/persistence of LVH (12.3% versus 15.8%, P=0.006) and of congestive heart failure (9.3% versus 15.4%, P<0.0001).

Conclusions—The ACE inhibitor ramipril decreases the development and causes regression of ECG-LVH independent of blood pressure reduction, and these changes are associated with reduced risk of death, myocardial infarction, stroke, and congestive heart failure. (Circulation. 2001;104:1615-1621.)

Key Words: hypertrophy ■ angiotensin ■ myocardium ■ cardiovascular diseases ■ risk factors ■ prevention

Electrocardiographic markers of left ventricular hypertrophy (LVH) predict poor cardiovascular prognosis.1,2 Treatment of systemic hypertension is associated with regression of ECG markers of LVH (ECG-LVH)3 and echocardiographic left ventricular mass.4–6 Several antihypertensive drugs including ACE inhibitors are effective in this regard.7 Whether regression or prevention of LVH will favorably modify the adverse prognosis is uncertain.8

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Ace inhibitors have a direct antihypertrophic effect on the myocardium and an antiproliferative effect on vascular smooth muscle.9 We therefore postulated that ACE inhibitors might prevent the development or cause regression of LVH independent of blood pressure reduction and that prevention or regression of ECG-LVH might be associated with reduced risk of adverse cardiovascular outcomes independent of blood pressure status or coronary artery disease.

There are few studies on the relation between measures of LVH and congestive heart failure (CHF). Data from the Heart Outcome Prevention Evaluation (HOPE) study show that ECG-LVH increases the risk of development of CHF in a broad range of patients who are at high risk without known left ventricular systolic dysfunction.2 However, it is unknown
whether prevention/regression of ECG-LVH would prevent the development of CHF in these patients.

We examined (1) whether treatment with ramipril prevented the development and caused regression of ECG-LVH in a wide range of patients with and without hypertension and with and without coronary artery disease (CAD) but without known left ventricular systolic dysfunction and (2) whether prevention and regression of ECG-LVH reduced the risk of cardiovascular morbidity, death, and development of CHF in these patients.

Methods

The HOPE study was a double-blind, placebo-controlled, international, multicenter, clinical trial primarily evaluating the effect of the ACE inhibitor ramipril and/or vitamin E with a 2 × 2 factorial design in preventing adverse cardiovascular events in patients who are at high risk without known left ventricular systolic dysfunction or CHF. Details of the rationale, methods,10 and the main outcomes have been published previously.11 A brief description follows.

Study Participants

Men and women 55 years of age or older with either known high-risk vascular disease or diabetes with at least 1 additional cardiovascular risk factor were eligible for enrollment. Additional risk factors in patients with diabetes mellitus included hypertension, dyslipidemia, cigarette smoking, and microalbuminuria. Exclusion criteria included CHF, known left ventricular ejection fraction of <40%, uncontrolled hypertension, and overt kidney disease. The participants were randomly assigned to receive 10 mg ramipril once daily or matching placebo. Investigators were encouraged to use antihypertensive agents other than ACE inhibitors to treat uncontrolled hypertension during the study.

Recruitment and Follow-Up

Participants were recruited from December 1993 to June 1995. Follow-up evaluations were done at 1 month from random assignment and every 6 months thereafter. The mean duration of follow-up was 4.5 years (range, 4 to 6 years). The institutional review board at each center approved the study, and all participants provided informed consent. An events adjudication committee blinded to randomization adjudicated all primary and secondary outcomes.

Definition of LVH

Participants had a 12-lead ECG at baseline, at 2 years, and at study end. LVH by ECG was considered to be present if the sum of the amplitudes of S wave in lead V1 and R wave in lead V5 or V6 exceeded 3.5 mV.12 LVH and strain pattern was considered to be present if there was ST-segment depression of at least 1 mm and inverted T wave in any lead in the direction opposite to the polarity of the QRS. Left-axis deviation was present if the frontal plane QRS axis was between −30° and −120°. To keep the definition simple and the results more applicable in large populations, only the voltage criterion for LVH (regardless of strain pattern or left-axis deviation) was used for all statistical analyses.

Participants who did not have at least 2 ECGs and whose ECGs were not interpretable for LVH were excluded from analysis. By definition, therefore, patients who died before the end of the second year were excluded. Local investigators interpreted the ECGs and reported the definitions satisfied for LVH; a copy of the ECG was forwarded to the data coordinating center.

Outcomes

The outcome variables were new development of LVH or lack of development (prevention) of LVH in participants without baseline LVH and persistence of LVH and disappearance (regression) of LVH in those who had baseline LVH. To maximize the follow-up period, the baseline ECG was compared with the study-end ECG when available (n=7457) or with the second-year ECG (n=824).

Preventing the development of LVH and causing regression of LVH are favorable effects; conversely, development of LVH and persistence of LVH are unfavorable. We compared prevention/regression of LVH and development/persistence of LVH in the placebo and the ramipril groups. Death and change in ECG-LVH status are competing end points; to avoid bias caused by differential mortality, we assessed the impact of ramipril on the composite outcome of death or change in LVH status. We also examined the impact of ramipril on ECG-LVH in predefined subgroups. To avoid bias caused by differential death, we assessed subgroup effect on the composite outcome of death or impact on LVH when appropriate.

We also compared cardiovascular outcomes in patients who had regression/prevention of LVH with those who had development/persistence of LVH. A composite of cardiovascular death, myocardial infarction, and stroke was defined a priori as the primary cardiovascular HOPE outcome.11 Each of these events were also recorded and analyzed separately. Prespecified secondary outcomes were hospitalization for CHF, hospitalization for unstable angina, revascularization procedures, and complications of diabetes. Other outcomes included death from any cause, unexpected (sudden) cardiac death, cardiac arrest, and CHF regardless of hospitalization.

Statistical Analysis

Baseline characteristics of patients with development/persistence versus prevention/regression of ECG-LVH were compared by means of χ² test for proportions and Student’s t test for continuous variables. A 2-sided P≤0.05 was considered statistically significant. We determined the effect of ramipril on prevention and regression of LVH by logistic regression analysis, allowing for baseline systolic blood pressure, baseline diastolic blood pressure, baseline presence of coronary artery disease, baseline presence of diabetes, and use of β-blockers and calcium channel blockers. We also assessed any impact of drop in systolic blood pressure (during the study) on the effect of ramipril on LVH with the use of a regression model. The effect of ramipril on regression/prevention of LVH in clinically relevant subgroups was determined by tests of interaction. Association between change in LVH status and outcome events was tested by χ². Nonfatal events, particularly myocardial infarction, occurring during the study might affect ECG-LVH status. To minimize their possible confounding effect on ECG-LVH, we did an additional analysis after excluding patients who had any outcome during the first 2 years of the study.

Results

Baseline Characteristics

There were 9541 participants in the HOPE Study. Of these, 8281 had 2 interpretable ECGs for comparison, one at baseline and another at study end (n=7457) or at 2 years (n=824). Among these 8281 participants, 676 had baseline ECG-LVH by voltage, of which 202 also had strain pattern, 152 had left-axis deviation, and 96 had strain pattern and left-axis deviation. Seven thousand six hundred five patients did not have baseline ECG-LVH. The baseline characteristics of patients who had development/persistence versus regression/prevention of ECG-LVH are compared in Table 1. The dose of ramipril or placebo was same in both groups.

Effect of Ramipril in Patients With LVH

At baseline, 321 patients in the ramipril group and 355 patients in the placebo group had ECG-LVH. Among these patients, 148 (46.1%) in the ramipril group compared with 137 (38.6%) in the placebo group had regression of ECG-LVH by the end of study (P=0.048, Table 2). The difference in regression between the ramipril group and placebo group remained significant after adjusting for possible confounding variables (P=0.045) (mentioned under Methods section).
Effect of Ramipril in Patients Without LVH

At baseline, 3814 patients in the ramipril group and 3791 patients in the placebo group did not have ECG-LVH. Among these patients, 163 (4.3%) in the ramipril group compared with 188 (5.0%) in the placebo group had LVH by the end of the study ($P=0.154$, Table 2). The combined outcome of death or development of LVH was significantly lower in the ramipril group (8.6%) than in the placebo group (11.0%, $P=0.0007$).

Effect of Ramipril in All Patients

Overall, 336 patients (8.2%) in the ramipril group compared with 406 patients (9.8%) in the placebo group had development/persistence of LVH; conversely, 3799 patients (91.9%) in the ramipril group compared with 3740 patients in the placebo group (90.2%) had regression/prevention of LVH ($P=0.008$), which remained significant after adjusting for possible confounding variables ($P=0.007$). The composite outcome of death or development/persistence of LVH was
significantly lower in the ramipril group (12.3%) than in the placebo group (15.4%, \( P = <0.0001 \), Table 2).

The effect of ramipril on LVH status remained significant after adjusting for drop in systolic blood pressure during the study (\( P = 0.005 \)). There was no confounding of the impact of ramipril on LVH by drop in systolic blood pressure (interaction coefficient = 0.275).

Effect of Ramipril on LVH in Subgroups
Patients randomly assigned to ramipril had a lower risk of development/persistence of ECG-LVH in all clinically relevant subgroups, with no qualitative interaction (Table 3). Conversely, regression/prevention of ECG-LVH was greater in the ramipril group in all subgroups of patients (Table, not shown).

There was a significant quantitative interaction on the effects of LVH by presence of CAD. Therefore we examined the interaction by presence of CAD on the combined outcome of death or change in LVH status. Among patients with CAD, 528 of 3392 (15.6%) in the placebo group compared with 440 of 3323 patients (13.2%) in the ramipril group died or had development/persistence of LVH (RR = 0.85; 95% CI, 0.76 to 0.96). Among patients without CAD, 111 of 754 (14.7%) in the placebo group compared with 67 of 812 (8.3%) in the ramipril group died or had development/persistence of LVH (RR = 0.56; 95% CI, 0.42 to 0.75). The interaction of CAD on this combined outcome remained significant (\( P = 0.032 \)).

### TABLE 2. Change in Status of ECG Markers of LVH in the Ramipril Group Compared With the Placebo Group

<table>
<thead>
<tr>
<th>Change in LVH* Status</th>
<th>Placebo, n (%)</th>
<th>Ramipril, n (%)</th>
<th>RR (95% CI) for Ramipril/Placebo</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with LVH at baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regression of LVH</td>
<td>137/355 (38.6)</td>
<td>148/321 (46.1)</td>
<td>1.20 (1.00–1.43)</td>
<td>0.048</td>
</tr>
<tr>
<td>Patients without LVH at baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Development of LVH</td>
<td>188/3791 (5.1)</td>
<td>163/3814 (4.3)</td>
<td>0.86 (0.70–1.06)</td>
<td>0.154</td>
</tr>
<tr>
<td>All patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Development/persistence of LVH</td>
<td>406/4146 (9.8)</td>
<td>336/4135 (8.1)</td>
<td>0.83 (0.72–0.95)</td>
<td>0.008</td>
</tr>
<tr>
<td>Regression/prevention of LVH</td>
<td>3740/4146 (90.2)</td>
<td>3799/4135 (91.9)</td>
<td>1.02 (1.01–1.03)</td>
<td></td>
</tr>
<tr>
<td>Death or development/persistence of LVH</td>
<td>639/4146 (15.4)</td>
<td>507/4135 (12.3)</td>
<td>0.80 (0.71–0.89)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*LVH denotes ECG markers of LVH.

### TABLE 3. Effect of Ramipril on Development/Persistence of LVH in Predefined Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Placebo, events/n (%)</th>
<th>Ramipril, events/n (%)</th>
<th>Relative Risk (95% CI)</th>
<th>( P ) for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of hypertension</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>3829</td>
<td>246/1880 (13.1)</td>
<td>221/1949 (11.3)</td>
<td>0.87 (0.73–1.03)</td>
</tr>
<tr>
<td>Absent</td>
<td>4452</td>
<td>160/2266 (7.0)</td>
<td>115/2186 (5.3)</td>
<td>0.75 (0.59–0.94)</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;139 mm Hg</td>
<td>4207</td>
<td>151/2098 (7.2)</td>
<td>129/2109 (6.1)</td>
<td>0.85 (0.68–1.07)</td>
</tr>
<tr>
<td>( \geq 139 ) mm Hg</td>
<td>4071</td>
<td>245/2041 (12.4)</td>
<td>207/2026 (10.2)</td>
<td>0.82 (0.69–0.98)</td>
</tr>
<tr>
<td>History of CAD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>6715</td>
<td>315/3392 (9.3)</td>
<td>287/3323 (8.6)</td>
<td>0.93 (0.80–1.08)</td>
</tr>
<tr>
<td>Absent</td>
<td>1566</td>
<td>91/754 (12.1)</td>
<td>49/812 (6.0)</td>
<td>0.50 (0.36–0.70)</td>
</tr>
<tr>
<td>History of diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>3102</td>
<td>160/1525 (10.5)</td>
<td>122/1577 (7.7)</td>
<td>0.74 (0.59–0.92)</td>
</tr>
<tr>
<td>Absent</td>
<td>5179</td>
<td>246/2621 (9.4)</td>
<td>214/2558 (8.4)</td>
<td>0.89 (0.75–1.06)</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>263</td>
<td>12/117 (10.3)</td>
<td>11/146 (7.5)</td>
<td>0.74 (0.34–1.60)</td>
</tr>
<tr>
<td>Absent</td>
<td>7990</td>
<td>392/4016 (9.8)</td>
<td>325/3974 (8.2)</td>
<td>0.84 (0.73–0.96)</td>
</tr>
<tr>
<td>( \beta )-Blockers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use</td>
<td>4944</td>
<td>241/2463 (9.8)</td>
<td>187/2481 (7.5)</td>
<td>0.77 (0.64–0.93)</td>
</tr>
<tr>
<td>No use</td>
<td>3337</td>
<td>165/1683 (9.8)</td>
<td>149/1654 (9.0)</td>
<td>0.92 (0.74–1.14)</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use</td>
<td>4680</td>
<td>204/2310 (8.8)</td>
<td>184/2370 (7.8)</td>
<td>0.88 (0.73–1.06)</td>
</tr>
<tr>
<td>No use</td>
<td>3589</td>
<td>201/1828 (11.0)</td>
<td>151/1761 (8.6)</td>
<td>0.78 (0.64–0.95)</td>
</tr>
</tbody>
</table>
Effect of Regression/Prevention of LVH on Cardiovascular Outcome

Nine hundred twenty-five (12.3%) of 7539 patients with regression/prevention of LVH had the primary outcome during the study period, compared with 117 (15.8%) of 742 patients with development/persistence of LVH (P=0.006). Patients with regression/prevention of LVH had a significantly lower incidence of cardiovascular death (3.4% versus 5.7%, P=0.001) or myocardial infarction (8.7% versus 10.9%, P=0.042), with a similar trend for stroke (3.45% versus 4.7%, P=0.079). The incidence of primary plus pre-specified secondary outcomes (hospitalization for CHF, hospitalization for unstable angina, revascularization procedures, and complications of diabetes) was significantly lower in patients with regression/prevention of LVH compared with those with development/persistence of LVH (32.5% versus 39.5%, P=0.0001). The risk of total death (5.4% versus 8.9%, P<0.0001) or of sudden death/cardiac arrest (1.9% versus 3.8%, P=0.0005) was also significantly lower in patients with regression/prevention compared with those with development/persistence of ECG-LVH (Table 4 and Figure).

The risk of development of congestive heart failure was substantially lower in patients with regression/prevention of LVH compared with those with development/persistence of LVH (9.3% versus 15.4%, P<0.0001; Table 4 and Figure).

Additional Analysis

After excluding patients who had any outcome before the end of the second year, 146 of 545 (26.8%) patients with development/persistence of LVH compared with 984 of 4311 (22.8%) patients with prevention/regression of LVH had the primary or secondary outcome (P=0.039). A similar trend was seen for the primary outcome alone: 71 of 627 (11.3%) in patients with development/persistence of LVH versus 475 of 4924 (9.7%) in those with prevention/regression of LVH (P=0.184).

Discussion

Regression/Prevention of LVH by Ramipril

This study shows that the ACE inhibitor ramipril causes regression and prevention of ECG-LVH in a broad range of patients with normal or controlled blood pressure with or without CAD. The impact of ramipril on LVH was independent of blood pressure reduction. Treatment of hypertension with various drugs has been shown to cause regression of LVH by echocardiogram.14,15 Although meta-analyses of studies have shown that ACE inhibitors are particularly effective,4 properly blinded comparisons show similar results with different blood pressure-lowering agents.7 In one study, a small number of patients with hypertension treated with the ACE inhibitor enalapril was found to have disappearance of ECG changes of LVH.14 In mild hypertension, lifestyle modifications such as weight reduction seem as effective, or more effective, than drug therapy.15 Before the present study, no intervention has been shown to prevent or cause regression of ECG-LVH in patients without hypertension or in hypertensive patients with controlled blood pressure. Prevention and regression of ECG-LVH by ramipril in a broad range of patients at high risk with or without hypertension and with or without CAD is a unique and important finding.

Regression of LVH in the Placebo Group

It is intriguing to note that regression of ECG-LVH also occurred in patients who were assigned to placebo. This could be related to a number of factors including multiple risk factor modification in patients who participate in clinical trials15,16 and use of concurrent medications such as β-blockers and other blood pressure-lowering drugs. This underscores the fact that only randomized, controlled trials such as the present one can provide proper evidence for change in LVH in response to an intervention.

Possible Mechanisms of LVH Regression by Ramipril

Both hemodynamic and neurohormonal mechanisms could be involved in regression/prevention of LVH by ramipril.8 A
further lowering of blood pressure in patients whose blood pressure is in the “normal range” may lead to prevention/regression of LVH. Furthermore, one may underestimate the degree of blood pressure reduction by relying on clinic measurements only. It is, however, important to note that the impact of ramipril on LVH in our patients was independent of hypertension and blood pressure reduction. Therefore, a direct antihypertrophic effect of ACE inhibitors seems probable, as demonstrated in animal studies.17,18

The lack of effect of ramipril on LVH in the presence of CAD is interesting. This is not fully explained by differential death of patients with CAD because the interaction on the composite end point of death or change in LVH status remains significant. The play of chance is not ruled out, but one possibility is that neurohormonal mechanisms might play a greater role in the pathophysiology of LVH in the absence of CAD and, therefore, ACE inhibitors might have a greater impact on LVH in this situation.

Effect of LVH Regression on Cardiovascular Outcome
Previous studies have established the utility of measures of LVH for cardiovascular prognosis. However, it is not certain whether regression of LVH will favorably modify this adverse prognosis.9 Changes in left ventricular mass by echocardiogram with treatment of hypertension appear to have prognostic implications.19 Also, estimates from predominantly hypertensive patients in the general population with LVH by ECG have shown an association between serial decrease in QRS voltage and lower risk of cardiovascular disease.3 Our study demonstrates that regression/prevention of ECG-LVH by ramipril is associated with reduced risk of cardiovascular morbidity and mortality in a broad range of patients who are at high risk, regardless of their blood pressure status and presence or absence of CAD.

Effect of LVH Regression on Development of CHF
ECG-LVH is common in patients with CHF1,20 and predicts the risk of development of CHF in patients at high risk.2 An important finding of the present study is that prevention and reversal of ECG-LVH by ramipril prevents the development of CHF in patients at high risk without known left ventricular systolic dysfunction regardless of their blood pressure status and presence or absence of CAD.

Kaplan-Meier estimates of outcomes in patients who had regression/prevention vs development/persistence of ECG markers of LVH. A, Primary outcome events (cardiovascular death, myocardial infarction, or stroke). B, Primary outcome events (cardiovascular death, myocardial infarction, or stroke) plus secondary outcome events (revascularization, hospitalization for unstable angina, hospitalization for CHF, and complications of diabetes). C, Unexpected (sudden) death or cardiac arrest. D, All CHF whether hospitalized or not.
Mechanism of Reversal of Adverse Cardiovascular Prognosis

LVH is a measure of sustained hemodynamic and/or neurohormonal stimulation on the myocardium, and so integrates the effect of these stimuli on the entire cardiovascular system. LVH is thus a marker not only of adverse cardiac events but also of other vascular events such as stroke and complications of peripheral vascular disease. It is therefore not surprising that prevention or reversal of ECG-LVH has a favorable effect on both cardiac and noncardiac vascular events.

Clinical Significance and Applicability

ECG-LVH and increased left ventricular mass by echocardiogram may not be the same,21 but both are strong predictors of prognosis,2,12,21,22 and the ECG has the advantage of simplicity and cost-effectiveness23; the ECG is recommended as a part of routine evaluation of patients with hypertension.24 Reduction of cardiovascular morbidity and mortality with reversal and prevention of ECG-LVH by ramipril in a broad range of patients at high risk with or without hypertension, with or without CAD, and without known left ventricular systolic dysfunction has great clinical importance and easy applicability.

Limitations

The ECGs were not centrally interpreted. Interpretation of ECGs by local investigators could compromise its accuracy. However, this should underestimate the clinical predictive value and have no material impact on the comparison between ramipril and placebo. In assessing the effect of ramipril on LVH, it is difficult to account for the impact of intercurrent events on LVH. This is avoided to some extent by excluding patients who died in the first 2 years and by additional analysis after excluding patients who had nonfatal outcome in the first 2 years.

Conclusions

Treatment with the ACE inhibitor ramipril causes regression and prevention of ECG-LVH in patients at high risk, independent of blood pressure levels and blood pressure reduction. This in turn is associated with reduced risk of adverse cardiovascular events, death, and CHF in these patients.

Acknowledgments

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