Effects of Telmisartan, Ramipril, and Their Combination on Left Ventricular Hypertrophy in Individuals at High Vascular Risk in the Ongoing Telmisartan Alone and in Combination With Ramipril Global End Point Trial and the Telmisartan Randomized Assessment Study in ACE Intolerant Subjects With Cardiovascular Disease

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Background—Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers reduce left ventricular hypertrophy (LVH). The effect of these drugs on LVH in high-risk patients without heart failure is unknown.

Methods and Results—In the Ongoing Telmisartan Alone and in Combination With Ramipril Global End Point Trial (ONTARGET), patients at high vascular risk and tolerant of ACE inhibitors were randomly assigned to ramipril, telmisartan, or their combination (n=23,165). In the Telmisartan Randomized Assessment Study in ACE Intolerant Subjects With Cardiovascular Disease (TRANSCEND), patients intolerant of ACE inhibitors were randomized to telmisartan or placebo (n=5,343). Prevalence of LVH at entry in TRANSCEND was 12.7%. It was reduced by telmisartan (10.5% and 9.9% after 2 and 5 years) compared with placebo (12.7% and 12.8% after 2 and 5 years) (overall odds ratio, 0.79; 95% confidence interval [CI], 0.68 to 0.91; P=0.0017). New-onset LVH occurred less frequently with telmisartan compared with placebo (overall odds ratio, 0.63; 95% CI, 0.51 to 0.79; P=0.0001). LVH regression was similar in the 2 groups. In ONTARGET, prevalence of LVH at entry was 12.4%. At follow-up, it occurred slightly less frequently with telmisartan (odds ratio, 0.92; 95% CI, 0.83 to 1.01; P=0.07) and the combination (odds ratio, 0.93; 95% CI, 0.84 to 1.02; P=0.12) than with ramipril, but differences between the groups were not significant. New-onset LVH was associated with a higher risk of primary outcome during follow-up (hazard ratio, 1.77; 95% CI, 1.50 to 2.07).

Conclusions—In patients at high vascular risk, telmisartan is more effective than placebo in reducing LVH. New-onset LVH is reduced by 37%. The effect of combination of the 2 drugs on LVH is similar to that of ramipril alone. (Circulation. 2009;120:1380-1389.)

Key Words: angiotensin • electrocardiography • epidemiology • hypertrophy • prognosis

Left ventricular hypertrophy (LVH) is a reversible determinant of cardiovascular risk, and its diagnosis may influence the therapeutic strategy. Echocardiography is more sensitive than ECG for the detection of LVH, but it is more expensive and dependent on geometrical assumptions that could reduce accuracy and reproducibility. Standard 12-lead ECG is recommended for the diagnosis of LVH in hypertensive subjects. LVH by ECG is a powerful predictor of...
cardiovascular morbidity and mortality in the general population\(^6\) and in selected groups of patients.\(^6,7\)

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ECG is also a diagnostic tool to detect serial changes in LVH.\(^5\) Several antihypertensive drugs, including diuretics,\(^8\) \(\beta\)-blockers,\(^9\) calcium channel blockers,\(^8\) angiotensin-converting enzyme (ACE) inhibitors,\(^10\) and angiotensin receptor blockers (ARBs),\(^11\) may cause regression of ECG LVH. ACE inhibitors may not completely block the production of angiotensin II, which is involved in the pathogenesis of LVH.\(^12\) Therefore, ARBs could differ from ACE inhibitors, and the combination of an ACE inhibitor and an ARB might be more effective than either alone. The Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET) and Telmisartan Randomized Assessment Study in ACE Intolerant Subjects With Cardiovascular Disease (TRANSCEND)\(^13,14\) enabled testing of these hypotheses. The 2 studies also offered the opportunity to test the relation between LVH and clinical outcome in a large, heterogeneous high-risk population. LVH assessment by ECG was a prespecified outcome of these studies.\(^15\)

**Methods**

Two multinational double-blind trials randomized patients at high cardiovascular risk without known LV systolic dysfunction or congestive heart failure to the ACE inhibitor ramipril, the ARB telmisartan, or their combination (in ONTARGET) or to telmisartan versus placebo (in TRANSCEND) in patients unable to tolerate ACE inhibitors. Background therapies were maintained. The median follow-up was 56 months. The main results of the studies have been published.\(^13,14\)

The primary end point was the composite of death resulting from cardiovascular causes, myocardial infarction, stroke, or hospitalization for congestive heart failure. Overall, 31,546 patients were randomized (ONTARGET, 25,620; TRANSCEND, 5926) with his-"
P<0.01) and more frequently female (33.6% versus 29.3%; P<0.01) than those included. In TRANSCEND, patients
excluded because of missing ECG data were balanced across
the 2 treatment groups by age (P=0.05), sex (P=0.33),
smoking (P=0.19), history of diabetes mellitus (P=0.48) and
coronary artery disease (P=0.49), and systolic (P=0.67) and
diastolic BPs (P=0.06). In ONTARGET, patients excluded
because of missing ECG data were also balanced across the
treatment groups by age (P=0.88), sex (P=0.31), smoking
(P=0.72), history of diabetes mellitus (P=0.51) and coronary
artery disease (P=0.15), and systolic BP (P=0.11), whereas
diastolic BP was slightly lower in the combination group
(81 mm Hg) than in each of the other groups (82 mm Hg;
P=0.03).

The main characteristics of patients included in the study
and divided by the presence or absence of LVH at entry are
reported in the Table. A consistent proportion of patients
received cardiovascular drugs. At the end of the study, 34%
were receiving diuretics, 58% were on β-blockers, 6% took
α1 blockers, 71% were receiving statins, and 36% took aspirin in addition to the study treatments.

Among the 3565 patients with LVH (12.5% of total
population), the diagnosis was based on abnormal voltages
alone in 51%, strain alone in 25%, and the combination of
both in 21%. Information on LVH components was missing
in 3% of patients. Atrial fibrillation or flutter was present at
entry in 3.1% of patients (4.6% with and 2.9% without LVH;
P<0.001). A pattern of right or left bundle-branch block was
found in 34.4% of subjects (27.2% with and 36.7% without
LVH; P<0.001). Pathological Q waves (≥0.04 second in
duration) on anterior leads were present in 30.0% of patients
(34.3% with versus 29.4% without LVH; P=0.003). Specif-
ically, the prevalence of LVH was 12.4% in ONTARGET
and 12.7% in TRANSCEND.

In TRANSCEND, the reduction in systolic BP from study
entry to follow-up averaged 6.6 mm Hg in the telmisartan
group and 2.5 mm Hg in the placebo group (mean difference,
4.1 mm Hg; P<0.0001). In ONTARGET, the reduction in
systolic BP averaged 6.9 mm Hg in the telmisartan group,
6.0 mm Hg in the ramipril group, and 8.5 mm Hg in the
combination group (∼1.0 mm Hg more with telmisartan
[P<0.001] and ∼2.5 mm Hg more with the combination
[P<0.001] compared with ramipril).

**Effects of Treatments on LVH**

**TRANSCEND: Comparison Between Telmisartan
and Placebo**

Prevalence of LVH at baseline (randomization) was 12.7% in
the telmisartan group and 12.8% in the placebo group
(P=0.86). After 2 and 5 years, it was 10.5% and 9.8% in the
telmisartan group and 12.7% and 12.8% with placebo (Figure
2). The odds of LVH on the total of available follow-up visits
was 21% lower in the telmisartan group than in the placebo
group (OR, 0.79; 95% CI, 0.68 to 0.91; P=0.0017). This difference remained significant after adjustment
for time of observation, achieved systolic BP, age,
history of diabetes mellitus and hypertension, baseline LVH,
and previous treatment with ACE inhibitors and ARBs (OR,
0.76; 95% CI, 0.64 to 0.90; P=0.0015).

Separate analyses were undertaken to investigate the
prevention and regression of LVH. In subjects without LVH at
entry (Figure 3), there was a 37% lower risk of LVH at
follow-up with telmisartan compared with placebo (OR, 0.63;
95% CI, 0.51 to 0.79; P=0.0001). This remained significant
after adjustment for time of observation, achieved systolic BP, age, history of diabetes mellitus and hypertension, and previous treatment with ACE inhibitors and ARBs (OR, 0.65; 95% CI, 0.52 to 0.81; \( P=0.0001 \)). The average reduction in systolic BP from entry to follow-up was greater in the subjects without than in those with future development of LVH (4.8 versus 1.8 mm Hg; \( P=0.0001 \)). In the subset with LVH at entry, there was in both groups a nonsignificant trend for less LVH at follow-up without significant differences between them (OR, 0.91; 95% CI, 0.70 to 1.19; \( P=0.49 \)). In this subset, the reduction in systolic BP from entry to follow-up was greater in the subjects with regression than in those with persistence of LVH (6.8 versus 3.9 mm Hg; \( P<0.0001 \)).

In sensitivity analyses, after the exclusion of patients with right or left bundle-branch block, the odds of LVH at follow-up remained 27% less in the telmisartan group than in the placebo group.
pathological Q waves, the odds of LVH at follow-up was 20% less in the telmisartan than in the placebo group ($P=0.005$).

**Subgroup Analyses**

The differences between telmisartan and placebo in TRANSCEND (Figure 4) were consistent across several prespecified subgroups.

**ONTARGET: Comparison Between Telmisartan, Ramipril, and Their Combination**

Figure 5 shows the prevalence of LVH at follow-up in the telmisartan, ramipril, and combination groups. LVH decreased from baseline to follow-up in all 3 groups (all $P<0.001$). LVH showed a nonsignificant trend to be less frequent with telmisartan than with ramipril (OR, 0.92; 95% CI, 0.83 to 1.01; $P=0.07$). The odds of LVH during follow-up was also nonsignificantly lower with the combination compared with ramipril (OR, 0.93; 95% CI, 0.84 to 1.02; $P=0.12$). We found no differences in the odds of LVH during the study between the telmisartan group and the combination group (OR, 1.01; 95% CI, 0.91 to 1.12).

**Relation Between LVH and Outcome**

In the total population, the risk of primary outcome during follow-up increased progressively (Figure 6) when the diagnosis of LVH at entry was based on high voltage alone (hazard ratio [HR], 1.41; 95% CI, 1.28 to 1.56; $P<0.001$), strain alone (HR, 1.71; 95% CI, 1.51 to 1.94; $P<0.001$), and their combination (HR, 2.15; 95% CI, 1.90 to 2.44; $P<0.001$) compared with the absence of LVH. Simultaneous adjustment for age, gender, diabetes mellitus, hypertension, and history of coronary artery disease did not change these estimates (all $P<0.001$).

In the subset of patients without LVH at entry, the primary study outcome (composite of death resulting from cardiovascular causes, myocardial infarction, stroke, and congestive heart failure requiring hospitalization) occurred more frequently in association with new-onset LVH at follow-up than in its absence (HR, 1.77; 95% CI, 1.50 to 2.07; $P<0.001$). The excess risk of primary outcome associated with new-onset LVH did not change after simultaneous adjustment for age, gender, and history of hypertension, diabetes mellitus, and coronary artery disease (HR, 1.67; 95% CI, 1.42 to 1.96; $P<0.001$). Figure 7 shows the modified Kaplan-Maier
curves reporting the incidence of primary outcome event in association with new-onset LVH.

Discussion

Our study on a widely heterogeneous population of subjects at high cardiovascular risk provides the following novel evidence. First, compared with placebo, which actually consisted of a group of subjects intensively treated with drugs other than those blocking the renin-angiotensin system, telmisartan was more effective in preventing the appearance of ECG-based LVH, whereas LVH regression was not affected. The effect on new-onset LVH remained significant when data were adjusted for factors including the treatment-induced reduction in BP and the previous exposure to blockers of the renin-angiotensin system. Second, in subjects randomized to telmisartan or to telmisartan combined with ramipril, the chance of LVH on follow-up was slightly lower than in subjects randomized to ramipril, although the differences were not statistically significant. The issues raised by these data are discussed below separately.

Figure 4. Odds of LVH in prespecified subgroups allocated to telmisartan or placebo. SBP indicates systolic BP; TIA, transient ischemic attack; and ACEI, ACE inhibitor.

Figure 5. Prevalence of LVH at baseline (randomization) and after 2 and 5 years in the groups randomized to telmisartan, ramipril, or their combination.
Telmisartan Versus Placebo

Although 21% fewer patients experienced LVH with telmisartan than with placebo in TRANSCEND, this difference did not translate into a difference in congestive heart failure, a complication predicted by LVH and its changes over time.\textsuperscript{11,18} Similarly, although 8% fewer patients experienced LVH with telmisartan than with ramipril in ONTARGET, this difference did not affect outcome. The modest reduction in BP at follow-up could explain the lack of significant differences between telmisartan and placebo on LVH regression, in contrast to the 37% lower risk of new-onset LVH in the telmisartan group compared with the placebo group. Of note, new-onset LVH was associated with a significantly higher risk of the primary study outcome in the total population regardless of randomized treatment. These findings extend to a mixed high-risk population the adverse prognostic impact of serial worsening in the ECG voltages or repolarization markers of LVH previously noted by the Framingham investigators in the general population.\textsuperscript{5} A further hypothesis to consider is that an improvement in the ECG markers of LVH might be less likely to occur in high-risk patients with severe atherosclerotic vascular disease and organ damage. In these patients, LVH regression might not translate to the same prognostic benefit as in the general population\textsuperscript{5} or in subjects with hypertension.\textsuperscript{18,19} The evidence provided by Okin and coworkers\textsuperscript{20} that the prognostic value of LVH regression is reduced in hypertensive patients with LVH and diabetes mellitus compared with those with LVH without diabetes mellitus is consistent with the above hypothesis.

Telmisartan Versus Ramipril

Telmisartan was associated with a statistically nonsignificant lower chance of LVH during follow-up compared with ramipril (\(-8\%\)). This was a posthoc analysis because the direct comparison between telmisartan and ramipril was not prespecified.\textsuperscript{15} In the few studies available, LVH regression was comparable with ACE inhibitors and ARBs.\textsuperscript{21,22} In a subset of 297 subjects included in ONTARGET who were studied with magnetic resonance imaging at baseline and
after 2 years, LV mass decreased to a similar extent in the 3 groups. LVH was absent in almost all these subjects at baseline (LV mass, 36.5 g/m²).\textsuperscript{23} One mechanism potentially leading to a greater LVH regression with an ARB compared with an ACE inhibitor might be the overactivation of AT2 subtype receptors by angiotensin II during treatment with an ARB. AT2 subtype receptors are upregulated in hypertrophic hearts.\textsuperscript{24} These receptors might trigger antiproliferative and antifibrotic effects, opposing AT1 receptor stimulation of cardiac hypertrophy and remodeling.\textsuperscript{25} Transgenic animals overexpressing AT2 subtype receptors showed less fibrosis than control animals in a model of occlusion/reperfusion of the left anterior descending artery.\textsuperscript{26}

**Telmisartan Plus Ramipril Versus Ramipril**

Patients allocated to the combination of telmisartan and ramipril showed a slightly lower, although not statistically significant, probability of LVH compared with ramipril alone. Hemodynamic and humoral factors associated with the decline in renal function, which was more pronounced in patients exposed to the dual blockade of renin-angiotensin system than in those treated with ramipril or telmisartan alone,\textsuperscript{27} might have limited the benefit of dual renin-angiotensin system blockade on LVH. Several mechanisms, including secondary hyperparathyroidism,\textsuperscript{28} abnormal vitamin D metabolism,\textsuperscript{29} activation of cardiac mineral corticoid receptors,\textsuperscript{30} and anemia,\textsuperscript{31} may be involved in the pathogenesis of LVH when renal function declines. ACE inhibitors, by inhibiting angiotensin II generation, could also limit the stimulating effect by angiotensin II on AT2 subtype receptors during treatment with an ARB, thereby limiting their protective impact on LVH.

**Voltage and Repolarization Markers of LVH and Clinical Outcome**

We found a progressive increase in the risk of primary study outcome when the diagnosis of LVH at entry was based on high voltages alone, strain alone, or their combination. Voltage-only LVH did not predict an increased risk of cardiovascular disease in general population studies.\textsuperscript{32} In the Heart Outcomes Prevention Evaluation (HOPE) study, which examined high-risk patients comparable to those enrolled in the present study, LVH defined by voltage alone was an independent predictor of outcome.\textsuperscript{33} In general population studies, which include a significant proportion of young and healthy subjects, elevated ECG voltages not accompanied by repolarization abnormalities might be more likely to identify relatively low-risk individuals characterized by less attenuation of voltages from the heart to the skin surface because of several potential factors, including a low body mass index and a younger age. Conversely, elevated ECG voltages could be more specific for true LVH in patients at higher risk. This issue warrants further investigation. The strain pattern was associated with a further increase in the risk of primary outcome. Concentric LVH has been associated with subendocardial ischemia both in the presence and in the absence of coronary artery disease.\textsuperscript{34} Frequency of strain increases in parallel with LV mass on echocardiography.\textsuperscript{35}

**Limitations**

Diagnosis of LVH was based on ECG, which is less sensitive than echocardiography.\textsuperscript{2} To simplify the calculation and obtain an adequate diagnostic performance, diagnosis of LVH by ECG was predefined by an index that incorporates voltage and repolarization criteria.\textsuperscript{17} Diagnosis of LVH was binary (yes/no), not quantitative. The product of ECG voltages (Cornell voltage) by QRS duration, which requires digital acquisition of tracings, provides an accurate estimate of LVH with the assessment of its changes in a quantitative fashion.\textsuperscript{36} Additionally, local investigators interpreted the ECGs using explicit prespecified criteria. Lack of precision in the ECG reading would likely be random and would not systematically bias the results. The degree of agreement between the central and investigators’ diagnoses of LVH in a randomly selected sample of 200 tracings was good, with a $\kappa$ statistic of 0.82. $\kappa$ Statistics between 0.61 and 0.80 have been defined as substantial, and those $>0.80$ have been defined as almost perfect.\textsuperscript{37} The peripheral reading of ECGs and the simple diagnostic criteria for LVH should increase the clinical applicability of our study.

**Conclusions**

Telmisartan was superior to placebo in preventing LVH in individuals at high vascular risk. This effect was independent of office BP changes. Office BP, however, may not reflect the BP burden over 24 hours. An ONTARGET/TRANSCEND substudy with 24-hour ambulatory BP monitoring\textsuperscript{15} will provide more insight into this issue. Telmisartan showed a trend to be slightly, but not significantly, more effective than ramipril in reducing ECG LVH, and the combination of the 2 drugs did not provide any additional benefit. The different pattern in LVH changes did not translate into a prognostic benefit, possibly because of the inadequate time for translation of the gradual LVH reduction into harder clinical events. These findings substantiate the efficacy of telmisartan in preventing the appearance of LVH in a wide population of patients at increased vascular risk.

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**Disclosures**

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**References**

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**CLINICAL PERSPECTIVE**

In patients with high vascular risk resulting from coronary artery disease, stroke, peripheral occlusive disease, or diabetes mellitus, the effect of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers on left ventricular (LV) hypertrophy (LVH) is unknown. In the Ongoing Telmisartan Alone and in Combination With Ramipril Global End Point Trial (ONTARGET), patients at high vascular risk and tolerant of angiotensin-converting enzyme inhibitors were randomly assigned to ramipril, telmisartan, or their combination. In the Telmisartan Randomized Assessment Study in ACE Intolerant Subjects With Cardiovascular Disease (TRANSCEND), telmisartan was more effective than placebo in preventing the appearance of ECG-based LVH (odds ratio, 0.63; 95% confidence interval, 0.51 to 0.79; *P*=0.0001), whereas LVH regression was not affected. In ONTARGET, LVH occurred slightly less frequently with telmisartan and the combination than with ramipril, but differences between groups were not significant. The risk of primary outcome during follow-up increased progressively when the diagnosis of LVH at entry was based on high voltage alone, strain alone, and their combination compared with the absence of LVH. New-onset LVH was associated with a higher risk of primary outcome during follow-up (hazard ratio, 1.77; 95% confidence interval, 1.50 to 2.07). Overall, these results are consistent with the main results of the study. The different pattern in LVH changes did not translate into a prognostic benefit, possibly because of the inadequate time for translation of the gradual LVH reduction into harder clinical events. These findings substantiate the efficacy of telmisartan in preventing the appearance of LVH in patients at increased vascular risk. The data also suggest that LVH defined on ECG by the combination of elevated voltages and strain is associated with a markedly increased risk in these patients.
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