Erectile Dysfunction Predicts Cardiovascular Events in High-Risk Patients Receiving Telmisartan, Ramipril, or Both

The ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial/Telmisartan Randomized Assessment study in ACE iNtolerant subjects with cardiovascular Disease (ONTARGET/TRANSCEND) Trials

Background—Although erectile dysfunction (ED) is associated with cardiovascular risk factors and atherosclerosis, it is not known whether the presence of ED is predictive of future events in individuals with cardiovascular disease. We evaluated whether ED is predictive of mortality and cardiovascular outcomes, and because inhibition of the renin-angiotensin system in high-risk patients reduces cardiovascular events, we also tested the effects on ED of randomized treatments with telmisartan, ramipril, and the combination of the 2 drugs (ONTARGET), as well as with telmisartan or placebo in patients who were intolerant of angiotensin-converting enzyme inhibitors (TRANSCEND).

Methods and Results—In a prespecified substudy, 1549 patients underwent double-blind randomization, with 400 participants assigned to receive ramipril, 395 telmisartan, and 381 the combination thereof (ONTARGET), as well as 171 participants assigned to receive telmisartan and 202 placebo (TRANSCEND). ED was evaluated at baseline, at 2-year follow-up, and at the penultimate visit before closeout. ED was predictive of all-cause death (hazard ratio [HR] 1.84, 95% confidence interval [CI] 1.21 to 2.81, \( P = 0.005 \)) and the composite primary outcome (HR 1.42, 95% CI 1.04 to 1.94, \( P = 0.029 \)), which consisted of cardiovascular death (HR 1.93, 95% CI 1.13 to 3.29, \( P = 0.016 \)), myocardial infarction (HR 2.02, 95% CI 1.13 to 3.58, \( P = 0.017 \)), hospitalization for heart failure (HR 1.2, 95% CI 0.64 to 2.26, \( P = 0.563 \)), and stroke (HR 1.1, 95% CI 0.64 to 1.9, \( P = 0.742 \)). The study medications did not influence the course or development of ED.

Conclusions—ED is a potent predictor of all-cause death and the composite of cardiovascular death, myocardial infarction, stroke, and heart failure in men with cardiovascular disease. Trial treatment did not significantly improve or worsen ED.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT 00153101.
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Key Words: trials † erectile dysfunction † cardiovascular diseases † drugs
angiotensin-receptor blocker (ARB) telmisartan has been shown to be noninferior to ramipril in reducing the risk of cardiovascular events. In those who are intolerant of ACE inhibitors, telmisartan has been found to be beneficial in reducing adverse cardiovascular outcomes. 

Clinical Perspective on p 1446

ED is associated with endothelial dysfunction in patients with cardiovascular risk factors and is associated with dysfunction of the endothelial progenitor cells involved in vascular repair. Angiotensin II produces endothelial dysfunction and is involved in detumescence of the human corpus cavernosum and thus is likely to be involved in ED. Several small studies have suggested that treatment with an ARB or ACE inhibitor is associated with improved erectile function and sexual performance in hypertensive and diabetic patients. Furthermore, it has been shown that treatment with an angiotensin II type 1 receptor antagonist reduces endothelial dysfunction in the corpus cavernosum while reducing atherosclerosis; however, it is not known whether such treatment will also improve ED. The Erectile Dysfunction Substudy of the ONTARGET (ONGoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) and TRANSCEND (Telmisartan Randomized Assessmetsnt Study in ACE iNitolerant subjects with cardiovascular Disease) trials was designed to determine whether ED is predictive of death and cardiovascular outcomes in high-risk patients with cardiovascular disease and whether telmisartan, ramipril, or their combination in these patients or telmisartan compared with placebo in ACE-inhibitor–intolerant patients had a beneficial effect on ED.

Methods

Study Design

The results of the main ONTARGET and TRANSCEND trials have been reported previously. In the ED substudy, 1549 of 22168 male patients participating in the trials were enrolled. They therefore shared the same eligibility criteria and study procedures, which have been described previously. The participating centers from the 13 countries taking part in the substudy asked all male patients for their consent to participate. The trial was coordinated and data were analyzed by the Population Health Research Institute at McMaster University/Hamilton Health Sciences, Hamilton, Ontario, Canada. Cardiovascular end points were adjudicated with the use of standard criteria by a central committee whose members were unaware of study group treatment assignments. The primary study outcome, which was based on the main ONTARGET and TRANSCEND trials, was a composite of death due to cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure. Other outcomes were death due to any cause and the individual components of the primary composite outcome.

A questionnaire was designed with previously validated instruments for ED detection. We used the 5-item short form of the International Index of Erectile Function (IIEF) and the Kölner (Cologne) Evaluation of Erectile Dysfunction scores. These evaluating tools were incorporated into 1 questionnaire as internal controls for each other. The Kölner Evaluation of Erectile Dysfunction score consists of 6 questions on a 5-point Likert scale as reported previously. An ascending score indicates worsening of ED, with a cutoff at >17 points for the diagnosis of ED. The IIEF score ranges from 5 to 25 points, in which a descending score indicates worsening of erectile function in patients, with a cutoff below 22 points for a diagnosis of ED. We have shown that evaluation of ED by use of these 2 methods yields similar results. In the present study, individuals scoring 5 to 7 points on the IIEF score were diagnosed as having severe ED, whereas 8 to 11 points indicated moderate ED, 12 to 16 points was mild to moderate ED, 17 to 21 points indicated mild ED, and 22 to 25 points signified no ED. These severity levels were used after the initial development and evaluation of the 5-item version of the IIEF score.

Questionnaires were given to consenting patients for self-completion at the run-in visit (baseline), after 2 years, and at the penultimate visit, which occurred at a median follow-up of 48 months. The questionnaires were returned to the study clinic in sealed envelopes, which were then forwarded to the Population Health Research Institute project office for processing. This approach was adopted to allow for patients’ sensitivity on these confidential issues. For patients who did not answer all questions but did answer at least 1 question, the weighted score of the respective answers was incorporated into the analysis. The substudy protocol was approved by the ethics committees of all local participating institutions.

Randomization and Follow-Up

Randomization procedures and medical treatments have been described in previous publications of the trials. Of the 1549 enrolled male patients, 400 patients were randomly assigned to ramipril, 395 to telmisartan, and 381 to combination therapy (ONTARGET). Among the ACE-intolerant patients (TRANSCEND), 202 patients were randomized to placebo and 171 to telmisartan. The run-in period and follow-up visit schedules were identical to those of the main trials. The median follow-up was 56 months for all patients in the main trials, 53 months for the ONTARGET ED substudy patients, and 54 months for the TRANSCEND ED substudy patients.

Statistical Analysis

Analysis was performed with SAS version 8.2 (SAS Institute, Cary, NC) on a Unix operating system. Continuous data are summarized by means and SDs. For nonnormally distributed variables, medians are also provided. Correlation coefficients were calculated with Spearman rank correlation. Categorical data are presented as actual frequencies and percentages. We compared the characteristics of patients who did not have ED (no or mild ED categories) with those who had ED (mild to moderate, moderate, and severe ED categories) and compared patients in the ED substudy with other male nonparticipating patients in ONTARGET/TRANSCEND using Student t tests or Wilcoxon rank sum test for continuous variables and the χ² test for categorical variables. The treatment effects on erectile function in terms of IIEF scores were compared with the Kruskal-Wallis test or Wilcoxon rank sum test. The treatment effect on time to onset of ED was analyzed by Cox regression. We determined the effect of baseline erectile function on the primary composite outcome, its components, and all-cause mortality by Cox regression analysis, stratifying by treatment allocation to account for combining the 2 studies and adjusting for age, systolic and diastolic blood pressure, smoking, history of hypertension, diabetes mellitus, myocardial infarction, stroke/transient ischemic attack, peripheral artery disease, lower urinary tract surgery, ankle-brachial index, alcohol consumption, and use of β-blockers and calcium channel blockers. Kaplan-Meier curves were used to estimate survival and were compared with the log-rank test. We used hazard ratios (with 95% confidence intervals) to examine the relationship of the severity of ED with subsequent clinical outcomes. A 2-tailed P<0.05 was considered statistically significant.

Results

Baseline Characteristics

Questionnaires were obtained from 1549 patients at baseline, at year 2, and at the penultimate follow-up visit; 89.3% of patients completed all questions, whereas 1.9% did not answer any of the questions and were not included in the analysis. Baseline characteristics of the 1519 patients who...
were enrolled in the substudy and who had baseline ED scores are summarized in Table 1. Patients with baseline ED were older and had a higher prevalence of hypertension, stroke/transient ischemic attack, diabetes, and lower urinary tract surgery than those without ED. Background medical therapy did not differ between those with and without ED except that calcium channel blockers were used more frequently in ED patients.

As in the main trials, the majority of patients had cardiovascular disease. Large proportions of patients had a previous myocardial infarction or stroke, and 34% of the patients had a history of diabetes. As in the main trials, these patients received high levels of proven therapies for cardiovascular risk reduction, which included statins, antiplatelet agents, ACE inhibitors or ARBs (before study enrollment), β-blockers, and diuretics, with no intergroup differences.

Correlation of ED Scores
Initial assessments of the Kölner Evaluation of Erectile Dysfunction and IIEF scores demonstrated that there was very close agreement in classification of ED in the participants (Spearman correlation $r=0.97$, $P<0.0001$ at baseline; $r=0.95$, $P<0.0001$ at year 2; and $r=0.96$, $P<0.0001$ at the penultimate visit), and for the purpose of the present report, data based on the IIEF scores only were used.

Prevalence of ED
The IIEF scores showed that there was a high prevalence of mild to moderate, moderate, or severe ED at entry (ramipril 57.6%, telmisartan-ONTARGET 54.4%, combination 52.7%, telmisartan-TRANSCEND 52.7%, and placebo 60.6%), with no significant differences among the treatment groups ($P=0.386$ for ONTARGET and $P=0.126$ for TRANSCEND).

Table 1. Baseline Characteristics of Patients

<table>
<thead>
<tr>
<th></th>
<th>ED Age, y</th>
<th>No. of Patients</th>
<th>Value</th>
<th>No. of Patients</th>
<th>Value</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP, mm Hg</td>
<td>840</td>
<td>140.8 (16.6)</td>
<td>677</td>
<td>139.2 (16.8)</td>
<td>0.063†</td>
<td></td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>840</td>
<td>81.7 (10.3)</td>
<td>677</td>
<td>82.5 (10.2)</td>
<td>0.163†</td>
<td></td>
</tr>
<tr>
<td>PP, mm Hg</td>
<td>840</td>
<td>59.0 (13.6)</td>
<td>677</td>
<td>56.7 (12.7)</td>
<td>0.0006†</td>
<td></td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>840</td>
<td>69.5 (12.7)</td>
<td>677</td>
<td>68.5 (11.7)</td>
<td>0.102†</td>
<td></td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td>840</td>
<td>4.95 (1.09)</td>
<td>673</td>
<td>4.85 (1.04)</td>
<td>0.074†</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>842</td>
<td>644 (76.5)</td>
<td>677</td>
<td>461 (68.1)</td>
<td>0.0003*</td>
<td></td>
</tr>
<tr>
<td>Stroke/TIA</td>
<td>842</td>
<td>241 (28.6)</td>
<td>677</td>
<td>149 (22.0)</td>
<td>0.003*</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>842</td>
<td>338 (40.1)</td>
<td>677</td>
<td>176 (26.0)</td>
<td>&lt;0.0001*</td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>842</td>
<td>418 (49.6)</td>
<td>677</td>
<td>372 (54.9)</td>
<td>0.040*</td>
<td></td>
</tr>
<tr>
<td>PAD</td>
<td>842</td>
<td>107 (12.7)</td>
<td>677</td>
<td>70 (10.3)</td>
<td>0.153*</td>
<td></td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>842</td>
<td>414 (49.2)</td>
<td>677</td>
<td>368 (54.4)</td>
<td>0.044*</td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td>842</td>
<td>102 (12.1)</td>
<td>675</td>
<td>92 (13.6)</td>
<td>0.380*</td>
<td></td>
</tr>
<tr>
<td>Physical activity  &gt;1/wk</td>
<td>842</td>
<td>601 (71.4)</td>
<td>677</td>
<td>495 (73.1)</td>
<td>0.452*</td>
<td></td>
</tr>
<tr>
<td>Education &gt;8 y</td>
<td>842</td>
<td>535 (63.5)</td>
<td>677</td>
<td>479 (70.8)</td>
<td>0.003*</td>
<td></td>
</tr>
<tr>
<td>Live with partner</td>
<td>840</td>
<td>684 (81.4)</td>
<td>674</td>
<td>583 (86.5)</td>
<td>0.008*</td>
<td></td>
</tr>
<tr>
<td>Location</td>
<td>Asia/Australia 842</td>
<td>296 (35.2)</td>
<td>677</td>
<td>197 (29.1)</td>
<td>0.004*</td>
<td></td>
</tr>
<tr>
<td>Europe</td>
<td>842</td>
<td>283 (33.6)</td>
<td>677</td>
<td>216 (31.9)</td>
<td>0.004*</td>
<td></td>
</tr>
<tr>
<td>Medications used</td>
<td>Statins</td>
<td>842</td>
<td>438 (52.0)</td>
<td>677</td>
<td>379 (56.0)</td>
<td>0.124*</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>842</td>
<td>481 (57.1)</td>
<td>677</td>
<td>395 (58.3)</td>
<td>0.633*</td>
<td></td>
</tr>
<tr>
<td>Diuretics</td>
<td>842</td>
<td>215 (25.5)</td>
<td>677</td>
<td>145 (21.4)</td>
<td>0.061*</td>
<td></td>
</tr>
<tr>
<td>α-Blocker</td>
<td>842</td>
<td>36 (4.3)</td>
<td>677</td>
<td>29 (4.3)</td>
<td>0.994*</td>
<td></td>
</tr>
<tr>
<td>CCB</td>
<td>842</td>
<td>364 (43.2)</td>
<td>677</td>
<td>232 (34.3)</td>
<td>0.0004*</td>
<td></td>
</tr>
<tr>
<td>LUTS</td>
<td>827</td>
<td>522 (63.1)</td>
<td>660</td>
<td>300 (45.5)</td>
<td>&lt;0.0001*</td>
<td></td>
</tr>
<tr>
<td>ABI abnormal</td>
<td>815</td>
<td>80 (9.8)</td>
<td>658</td>
<td>71 (10.8)</td>
<td>0.540*</td>
<td></td>
</tr>
</tbody>
</table>

SBP indicates systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; MI, myocardial infarction; PAD, peripheral artery disease; CCB, calcium channel blocker; LUTS, lower urinary tract symptoms; and ABI, ankle-brachial index.

Values are mean (SD) [median] for continuous variables or n (%) for categorical variables.

*χ² Test.
†Student t test for normally distributed variables or Wilcoxon rank-sum test for nonnormally distributed variables.
Follow-Up, Study Adherence, and Side Effects

Of the 1549 patients initially enrolled in the substudy, 1 patient in the ramipril arm of ONTARGET and 1 patient in the placebo arm of TRANSCEND were lost to follow-up. Adherence to study medications by patients in all groups was high. Most patients continued taking full doses, with small proportions receiving reduced doses during the study. In the ONTARGET arm, 61 patients (15.3%) taking ramipril, 43 (10.9%) taking telmisartan, and 61 (16.0%) taking the combination thereof permanently discontinued taking study medications \((P=0.183)\), as did 19 (11.1%) taking telmisartan and 31 (15.4%) taking placebo \((P=0.232)\) in the TRANSCEND arm. The full dose (or reduced doses, in parentheses) of study ramipril was taken by 87.6% (5.3%) and 83.9% (5.7%) at 2 years and at the penultimate visit, respectively. For ONTARGET, the proportions taking full (or reduced) doses at 2 years and at the penultimate visit, respectively, were 95.1% (0.26%) and 91.3% (0.54%) for telmisartan; for the combination, the percentages were 82.9% (8.7%) and 79.5% (8.7%) for ramipril and 94.0% (0.54%) and 89.6% (1.4%) for telmisartan. For telmisartan in TRANSCEND, the percentages of patients taking full (reduced) doses at 2 years and at the penultimate visit, respectively, were 93.5% (1.9%) and 87% (3.1%) at 2 years and at the penultimate visit, respectively, whereas for placebo, the percentages were 94.9% (0%) and 86.4% (0%), respectively. Symptomatic hypotension was experienced more often in the group taking combination therapy, with 11 patients (2.9%) experiencing hypotension versus 3 (0.8%) in the ramipril-only arm \((P=0.024)\); a cough was more common in the ramipril-only arm, occurring in 8 patients (2.0%), as well as in 10 patients (2.6%) in the combination-therapy arm, compared with 1 patient (0.3%) in the telmisartan-only arm (both \(P=0.02)\).

Blood Pressure Reduction

In ONTARGET, blood pressure-lowering effects were different between the treatment groups (average mean systolic blood pressure reduction 7.6 mm Hg for telmisartan, 5.4 mm Hg for ramipril, and 8.5 mm Hg for the combination arm; \(P=0.015\)), with no significant difference between the telmisartan and combination arms \((P=0.651)\); however, the decrease in systolic blood pressure was greater with the combination than with ramipril alone \((P=0.01)\). In TRANSCEND, there was greater blood pressure lowering in the telmisartan group than with placebo (average mean systolic blood pressure reduction 6.7 mm Hg for telmisartan and 1.2 mm Hg for placebo, \(P=0.0002)\).

Cardiovascular Events in Patients With or Without Baseline ED

All-cause deaths occurred in 11.3% of the patients who reported ED at baseline but only in 5.6% of patients with no or mild ED at baseline (hazard ratio 2.04, 95% confidence interval 1.40 to 2.97, \(P=0.0002)\). The composite primary outcome of cardiovascular death, myocardial infarction, stroke, and heart failure hospitalization occurred in 16.2% of patients with ED, which represents a hazard ratio of 1.62 (95% confidence interval 1.22 to 2.17, \(P=0.001)\) compared with 10.3% of
patients with no or mild ED at baseline. Patients with ED at baseline also were more likely to die of cardiovascular causes ($P = 0.0009$) or myocardial infarction ($P = 0.04$). Patients reporting ED tended to have higher risks for heart failure and stroke, but the observed trends toward increased risk were not significantly different (Figure 1). The hazard ratio associated with ED for the above outcomes largely remained consistent after appropriate adjustment for the potential confounders as described above under “Statistical Analysis” (Figure 1).

Compared with participants not reporting ED, the incidence of all-cause death, as indicated by the survival curves (Figure 2A), was increased in patients with baseline ED ($P = 0.0001$). The same difference was observed for the composite primary outcome of cardiovascular death, myocardial infarction, stroke, and heart failure hospitalization in patients reporting ED at baseline compared with those without ED ($P = 0.0008$; Figure 2B). For the individual components of the primary outcome, there was a significant difference in cardiovascular death ($P = 0.0006$; Figure 2C) and myocardial infarction ($P = 0.046$; Figure 2D). There were nonsignificant trends for hospitalization for heart failure or stroke (Figure 2E and 2F).

Figure 3 shows the risk for all-cause deaths and primary composite outcome by grade of ED with the IIEF scores as the categorical variable by combining, at baseline, the groups with mild to moderate and moderate ED as 1 group and using those with severe ED as the other group and the no-ED/mild group as the referent. The risks increased in a stepwise manner with progression of ED.

Effects of Treatment on Erectile Function
To identify the effects of the study pharmacological treatments on ED, the IIEF scores at run-in, year 2, and the penultimate visits were compared in patients treated with
ramipril, telmisartan, or their combination in ONTARGET, whereas for TRANSCEND, telmisartan was compared with placebo. As shown in Tables 2 and 3, there were no significant differences in IIEF scores or the changes in scores at the run-in, 2-year, and penultimate visits among the treatment groups in either ONTARGET or TRANSCEND. Over time, there were also no differences in onset of new ED due to either treatment (compared by Cox regression analysis for time to onset of ED). Furthermore, there were no significant differences among the treatment arms in either ONTARGET or TRANSCEND. At the run-in, 2-year, and penultimate visits among the treatment groups in either ONTARGET or TRANSCEND. Over time, there were also no differences in onset of new ED due to either treatment (compared by Cox regression analysis for time to onset of ED). Furthermore, there were no significant differences among the treatment arms in either trial for all-cause deaths, the composite primary outcome, or vascular events.25,26 Therefore, it was reasonable to assume advanced atherosclerosis and is predictive of future cardiovascular events.25 Also, endothelial dysfunction is a predictor of cardiovascular events in high-risk cardiovascular patients, as well as that oxidative stress in the vascular wall is associated with activation of the renin-angiotensin system.13,25 Although many trials in high-risk patients have shown that modulation of the renin-angiotensin system leads to reduced cardiac events in patients with heart failure, high vascular risk, or hypertension, no study has assessed the impact of renin-angiotensin system modulation on ED.6–9

In the present study, we evaluated prospectively whether ED, as a potentially clinically relevant symptom of endothelial dysfunction, was related to death and cardiovascular events. We also examined whether treatment with the ACE inhibitor ramipril and/or the ARB telmisartan, both of which were effective in reducing cardiovascular events, would improve erectile function. In the present study, the association of ED at baseline with subsequent major cardiovascular events was studied in 1519 male patients of the ONTARGET and TRANSCEND trials. In this population, ED was highly prevalent, occurring in 55% of patients. This was approximately twice as high as its prevalence in a general population.21,22,26

Values are median and mean (SD). Treatment effects were compared by use of absolute IIEF scores and changes in IIEF scores at different time points of follow-up.

*By Wilcoxon rank sum test.

Table 3. Effects of Treatment on Erectile Function in TRANSCEND

<table>
<thead>
<tr>
<th>IIEF score</th>
<th>Placebo</th>
<th>Telmisartan</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>At run-in</td>
<td>15; 15.07 (5.91)</td>
<td>16; 16.04 (6.12)</td>
<td>0.093</td>
</tr>
<tr>
<td>No. of patients</td>
<td>198</td>
<td>169</td>
<td></td>
</tr>
<tr>
<td>At year 2</td>
<td>13; 14.05 (4.11)</td>
<td>14; 14.37 (4.46)</td>
<td>0.440</td>
</tr>
<tr>
<td>No. of patients</td>
<td>167</td>
<td>148</td>
<td></td>
</tr>
<tr>
<td>At penultimate visit</td>
<td>13; 14.33 (4.27)</td>
<td>14; 14.70 (4.65)</td>
<td>0.630</td>
</tr>
<tr>
<td>No. of patients</td>
<td>125</td>
<td>104</td>
<td></td>
</tr>
<tr>
<td>Change in IIEF score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 2 to run-in</td>
<td>0; −0.96 (4.87)</td>
<td>−2; −1.52 (5.18)</td>
<td>0.249</td>
</tr>
<tr>
<td>No. of patients</td>
<td>163</td>
<td>147</td>
<td></td>
</tr>
<tr>
<td>Penultimate visit to run-in</td>
<td>−1; −0.74 (5.08)</td>
<td>−1; −1.45 (4.69)</td>
<td>0.348</td>
</tr>
<tr>
<td>No. of patients</td>
<td>121</td>
<td>103</td>
<td></td>
</tr>
<tr>
<td>Penultimate visit to year 2</td>
<td>0; 0.17 (3.90)</td>
<td>0; 0.76 (4.70)</td>
<td>0.834</td>
</tr>
<tr>
<td>No. of patients</td>
<td>121</td>
<td>99</td>
<td></td>
</tr>
</tbody>
</table>

Values are median and mean (SD) unless otherwise indicated. Treatment effects were compared by use of absolute IIEF scores and changes in IIEF scores at different time points of follow-up.

*By Wilcoxon rank sum test.

Discussion

A close correlation between cardiovascular risk factors, preexisting cardiovascular disease, and ED has been shown previously in registries and cross-sectional studies.3,10,21,22 ED is believed to be due to endothelial dysfunction and oxidative stress in tissues of the corpus cavernosum and penile arteries.24 It is known that endothelial dysfunction is a predictor of cardiovascular events in high-risk cardiovascular patients, as well as that oxidative stress in the vascular wall is associated with activation of the renin-angiotensin system.13,25 Although many trials in high-risk patients have shown that modulation of the renin-angiotensin system leads to reduced cardiac events in patients with heart failure, high vascular risk, or hypertension, no study has assessed the impact of renin-angiotensin system modulation on ED.6–9

In the present study, we evaluated prospectively whether ED, as a potentially clinically relevant symptom of endothelial dysfunction, was related to death and cardiovascular events. We also examined whether treatment with the ACE inhibitor ramipril and/or the ARB telmisartan, both of which were effective in reducing cardiovascular events, would improve erectile function. In the present study, the association of ED at baseline with subsequent major cardiovascular events was studied in 1519 male patients of the ONTARGET and TRANSCEND trials. In this population, ED was highly prevalent, occurring in 55% of patients. This was approximately twice as high as its prevalence in a general population.21,22,26

Endothelial dysfunction is associated with ED.10,24 It is also an early pathophysiological step in the pathogenesis of advanced atherosclerosis and is predictive of future cardiovascular events.25,26 Therefore, it was reasonable to assume that ED was related to cardiovascular outcomes and possibly both cardiovascular-related and all-cause death. The present data clearly show that ED is closely associated with an increased risk for all-cause deaths, as well as the primary
composite outcome of cardiovascular death, myocardial infarction, stroke, and hospitalization for heart failure. It is likely that the presence of ED identifies individuals whose cardiovascular disease might be far more advanced than evaluated by other clinical parameters alone. The present results are similar to the findings in a group of diabetic subjects in another study in whom ED was strongly associated with major adverse cardiac events compared with patients with no ED. The association was particularly close with regard to all-cause and cardiovascular death. According to the IIEF scores in the present study, there was an increased risk in patients with mild to severe ED, and we observed a stepwise increase in risk depending on the severity of ED. It is concluded that ED is a powerful predictor of cardiovascular death and of major cardiovascular events in high-risk patients and represents a symptom of more advanced atherosclerosis and endothelial dysfunction.

Angiotensin II is synthesized in the corpus cavernosum, is involved in detumescence of the corpus cavernosum, and produces oxidative stress in the penile endothelium, thereby possibly promoting the development of ED. In hypertensive apolipoprotein E knockout mice, endothelial function of the corpus cavernosum as a surrogate for ED was improved in tandem with a reduction in aortic plaque load by ARB treatment. A crossover clinical study in hypertensive couples revealed a significant increase in sexual intercourse frequency per month with use of an ARB compared with carvedilol. Observational studies showed an increase in sexual activity in hypertensive subjects or patients with the metabolic syndrome who were treated with ACE inhibitors or ARB compared with those given other standard therapies or β-blockers. However, in the present TRANSCEND ED substudy, telmisartan showed only an insignificant trend to improve ED compared with placebo. There were no differences between treatment arms in ONTARGET, but there was no evidence for an adverse effect of the treatments on erectile function. Therefore, as with clinical cardiovascular end points, telmisartan was not superior to ramipril nor was their combination superior to ramipril alone with regard to the development of ED. There was no evidence that the treatments would prevent the development of ED in those participants without baseline ED or that they would reverse ED in those with preexisting ED.

In conclusion, the present study shows that in high-risk cardiovascular patients, ED is highly predictive of all-cause deaths and the composite of cardiovascular deaths, myocardial infarction, stroke, and heart failure. Proven risk-reducing medications such as ramipril, telmisartan, and the combination thereof did not have different effects on ED, but neither treatment adversely affected erectile function. The evaluation of ED in the medical history as an early symptom of endothelial dysfunction and atherosclerosis and as a predictor of death and future cardiovascular events might be relevant to identify patients at particularly high risk of experiencing a cardiovascular event.

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References


**CLINICAL PERSPECTIVE**

The prevalence of erectile dysfunction is 20% to 30% in the general population but increases to more than 50% in the cardiovascular high-risk population of the ONTARGET/TRANSCEND trials, who are commonly encountered in clinical practice. Moreover, erectile dysfunction is associated with cardiovascular risk factors owing to the physiology of penile erection, which is crucially dependent on endothelial function and nitric oxide synthesis. The prospective erectile dysfunction substudy of the ONTARGET/TRANSCEND trials shows for the first time that erectile function is a predictor of cardiovascular morbidity and mortality. These results remained after adjustment for possible confounders. Thus, erectile dysfunction represents an early symptom of endothelial dysfunction and atherosclerosis, and patients with erectile dysfunction are at a particularly high cardiovascular risk. The identification of these patients with erectile dysfunction offers the opportunity for early risk-adjusted treatment with the goal of further reducing cardiovascular events.
Erectile Dysfunction Predicts Cardiovascular Events in High-Risk Patients Receiving Telmisartan, Ramipril, or Both: The ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial/Telmisartan Randomized AssessmentNt Study in ACE iNtolerant subjects with cardiovascular Disease (ONTARGET/TRANSCEND) Trials

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Supplemental Material

Appendix

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