Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomised controlled trial

The Telmisartan Randomised AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease (TRANSCEND) Investigators*

Summary

Background Angiotensin-converting enzyme (ACE) inhibitors reduce major cardiovascular events, but are not tolerated by about 20% of patients. We therefore assessed whether the angiotensin-receptor blocker telmisartan would be effective in patients intolerant to ACE inhibitors with cardiovascular disease or diabetes with end-organ damage.

Methods After a 3-week run-in period, 5926 patients, many of whom were receiving concomitant proven therapies, were randomised to receive telmisartan 80 mg/day (n=2954) or placebo (n=2972) by use of a central automated randomisation system. Randomisation was stratified by hospital. The primary outcome was the composite of cardiovascular death, myocardial infarction, stroke, or hospitalisation for heart failure. Analyses were done by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00153101.

Findings The median duration of follow-up was 56 (IQR 51–64) months. All randomised patients were included in the efficacy analyses. Mean blood pressure was lower in the telmisartan group than in the placebo group throughout the study (weighted mean difference between groups 4·0/2·2 [SD 19·6/12·0] mm Hg). 465 (15·7%) patients experienced the primary outcome in the telmisartan group compared with 504 (17·0%) in the placebo group (hazard ratio 0·92, 95% CI 0·81–1·05, p=0·216). One of the secondary outcomes—a composite of cardiovascular death, myocardial infarction, or stroke—occurred in 384 (13·0%) patients on telmisartan compared with 440 (14·8%) on placebo (0·87, 0·76–1·00, p=0·048 unadjusted; p=0·068 after adjustment for multiplicity of comparisons and overlap with primary outcome). 894 (30·3%) patients receiving telmisartan were hospitalised for a cardiovascular reason, compared with 980 (33·0%) on placebo (relative risk 0·92, 95% CI 0·85–0·99; p=0·025). Fewer patients permanently discontinued study medication in the telmisartan group than in the placebo group (639 [21·6%] vs 705 [23·8%]; p=0·055); the most common reason for permanent discontinuation was hypotensive symptoms (29 [0·98%] in the telmisartan group vs 16 [0·54%] in the placebo group).

Interpretation Telmisartan was well tolerated in patients unable to tolerate ACE inhibitors. Although the drug had no significant effect on the primary outcome of this study, which included hospitalisations for heart failure, it modestly reduced the risk of the composite outcome of cardiovascular death, myocardial infarction, or stroke.

Funding Boehringer Ingelheim.

Introduction Angiotensin-converting enzyme (ACE) inhibitors reduce mortality, myocardial infarction, stroke, and heart failure in patients with cardiovascular disease or high-risk diabetes.1–3 However, up to about 20% of patients—particularly women or Asians—are unable to tolerate an ACE inhibitor, mainly due to cough, but also due to hypotensive symptoms, renal dysfunction, or angio-neurotic oedema.4–5 Angiotensin-receptor blockers are similar in efficacy and are better tolerated than ACE inhibitors in high-risk patients after myocardial infarction,6 or in those with cardiovascular disease or high-risk diabetes.7 Angiotensin-receptor blockers reduce mortality and rehospitalisation for heart failure, compared with placebo, in patients intolerant to ACE inhibitors with low ejection fraction and heart failure,8–9 and also reduce stroke and cardiovascular morbidity compared with β blockers, in those with moderate hypertension and left ventricular hypertrophy.10 However, direct evidence of benefit of an angiotensin-receptor blocker in reducing major cardiovascular events in broader high-risk populations is lacking.

In the Telmisartan Randomised AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease (TRANSCEND), we investigated whether an angiotensin-receptor blocker—telmisartan—given long term, reduces cardiovascular death, myocardial infarction, stroke, or hospitalisation for heart failure in patients with cardiovascular disease or high-risk diabetes and without heart failure, who are intolerant to ACE inhibitors, compared with placebo, in addition to other usual therapies.11
Methods

Patients

The design of the ONGoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) programme has been described in detail elsewhere. Briefly, patients intolerant to ACE inhibitors were enrolled if they had established coronary artery, peripheral vascular or cerebrovascular disease, or diabetes with end-organ damage. Intolerance to ACE inhibitors was defined as previous discontinuation by a physician because of intolerance, with a specific documented cause. Patients were excluded if there was a need for or inability to discontinue angiotensin-receptor blockers, or known hypersensitivity or intolerance to these drugs. We excluded patients with heart failure, significant primary valvular or cardiac outflow tract obstruction, constrictive pericarditis, complex congenital heart disease, unexplained syncope, planned cardiac surgery or cardiac revascularisation within the previous 3 months, systolic blood pressure over 160 mm Hg, heart transplantation, subarachnoid haemorrhage, significant renal artery stenosis, creatinine levels above 265 μmol/L, proteinuria, or hepatic dysfunction.

National coordinators and clinical monitors supervised recruitment in 630 centres in 40 countries. The study was coordinated at the Population Health Research Institute, McMaster University, and Hamilton Health Sciences, with sub-offices at the University of Oxford and University of Auckland. The steering committee designed and oversaw the trial. An operations committee, with representatives from the three coordinating centres and the sponsor met regularly. The protocol was approved by the appropriate regulatory authorities and the ethics review committee at each participating institution. All participants gave written informed consent.

Procedures

Eligible patients were entered into a single blind run-in involving placebo daily for a week followed by 2 weeks of telmisartan 80 mg. At the end of this run-in period, patients were randomised in a one to one ratio by use of a central automated randomisation system to receive telmisartan (80 mg/day) or placebo. Randomisation was stratified by hospital. Both patients and trialists were blinded to treatment allocation.

The primary outcome was the composite of cardiovascular death, myocardial infarction, stroke, or hospitalisation for heart failure. Secondary outcomes were the composite outcome of cardiovascular death, myocardial infarction, or stroke (the primary outcome of the Heart Outcomes Prevention Evaluation [HOPE] trial). Other secondary outcomes included new heart failure, development of diabetes mellitus, atrial fibrillation, cognitive decline or dementia, nephropathy, and revascularisation. Other outcomes were total mortality, angina, transient ischaemic attack, development of left ventricular hypertrophy, microvascular complications of diabetes, changes in blood pressure, changes in ankle-to-arm blood pressure ratios, and new cancers. We also assessed the combined outcome of macrovascular and microvascular disease used in the Action in Diabetes and Vascular Disease: preterAx and diamicroN Controlled Evaluation (ADVANCE) trial.

Patients were assessed at follow-up visits scheduled at 6 weeks and 6 months, and then every 6 months. All primary outcome events and deaths were adjudicated, using standardised criteria, by a blinded central committee. Since most of the patients had pre-existing cardiovascular disease, deaths were classified as due to cardiovascular causes unless an unequivocal non-cardiovascular cause was established. Acute myocardial infarction was defined by creatine kinase levels twice the normal upper limit, creatine-kinase-MB above normal or troponin T or I levels above the definite abnormal (necrotic) range for the laboratory, except after a percutaneous coronary intervention (creatine kinase MB >3 times normal upper limit), or coronary bypass graft surgery (creatine kinase MB >10 times normal upper limit). Additionally, a patient had to have new Q waves (or new prominent R waves in V1 or V2 indicating the presence of posterior myocardial infarction), new left bundle branch block, or ischaemic ST-T changes in an electrocardiograph, or typical clinical presentation consistent with myocardial infarction. Stroke was defined as new focal neurological deficits thought to be of vascular origin with signs or symptoms lasting longer than 24 h, or death if this occurred earlier. Hospitalisation for heart failure was defined as hospitalisation for heart failure or attendance in an acute care setting, with two of the three criteria: administration of intravenous diuretic, escalation of diuretic doses or inotropes, or radiological evidence of heart failure.
Statistical analysis
The sample size was estimated from the rate of cardiovascular death, myocardial infarction, stroke, or hospitalisation for heart failure derived from the HOPE trial. An overall sample size of 6000 patients was expected to have 94% power to detect a hazard ratio of 0·81 for telmisartan compared with placebo at a two-sided alpha of 0·05, assuming a control hazard rate of 0·0512 per year in the control group, a recruitment period of 2 years, and a maximum observation time of 5·5 years.

The primary analysis included all randomised patients and used a time-to-event approach, counting the first occurrence of any component of the composite outcome. All p values are two sided. Adjustments for differences in blood pressure for the primary and secondary time-to-event analysis were made by inclusion of the most recent systolic blood pressure before the event (for patients with events) or before the last date of follow-up (in patients without events) as a covariate in the model. Consistency of treatment effects in prespecified subgroups was explored by Cox regression model, with tests for interaction. Before the completion of the Prevention Regimen For Effectively avoiding Second Strokes (ProFESS) trial and TRANSCEND, we had specified that a combined analysis of the data from the two trials would be done using a modified Mantel-Haenzel method.

An independent data and safety monitoring board of cardiologists, statisticians, and clinical trial experts met twice yearly. There were three formal interim analyses, when 25%, 50%, and 75% of the events had accrued. A modified Haybittle-Peto approach, with a boundary of 4 SD in the first half and 3 SD in the second half of the trial, guided decisions regarding efficacy. For safety, the boundaries were reduced to 3 SD and 2 SD, respectively.

Role of the funding source
The study was designed and conducted by the steering committee. The study sponsor received the data only after the study had been completed. All data were received, checked, and analysed independently by the Population Health Research Institute. All statistical analyses for this paper were done by staff at this institute. The corresponding author had full access to all data in the study and had final responsibility to submit this manuscript for publication.

Results
The trial profile is shown in figure 1. Patients were enrolled between November, 2001, and May, 2004. At the end of the run-in period, 874 (29·6%) patients randomised to receive telmisartan and 899 (30·2%) to placebo were receiving, or had previously received, an angiotensin-receptor blocker. Of the randomised population, the most common reason for intolerance to ACE inhibitors was cough (5225 participants, 88·2%), followed by...
symptomatic hypotension (244, 4·1%), angio-oedema or anaphylaxis (75, 1·3%), renal dysfunction (58, 1·0%), and other reasons (492, 8·3%).

The characteristics of the randomised patients were similar in both treatment groups (table 1). The mean age of the randomised patients was 66·9 (SD 7·3) years; 2547 (43·0%) were women, 4528 (76·4%) had hypertension, and 2118 (35·7%) had diabetes. Mean blood pressure was 141·0 (SD 16·6)/81·9 (10·1) mm Hg, fasting plasma glucose was 6·0 (SD 5·0) mmol/L, and total cholesterol was 5·0 (1·6) mmol/L. Many of the patients were on proven therapies.

The median duration of follow-up was 56 (IQR 51–64) months. Vital status was ascertained in 5908 (99·7%) patients at the end of the study. Of the 2122 (80·8%) patients taking telmisartan at the end of the study, 2086 (79·4%) were on the full dose, with only 36 (1·4%) on reduced dose. Non-study angiotensin-receptor blockers were used in 54 (1·8%) patients in the telmisartan group and 84 (2·9%) in the placebo group at 1 year, increasing to 152 (5·8%) and 200 (7·6%) by the end of the study. Other non-study blood-pressure-lowering agents were used more frequently in the placebo group than in the telmisartan group by the end of the study (telmisartan vs placebo—diuretics: 888 [33·7%] vs 1059 [40·0%], p<0·0001; calcium channel blockers: 1003 [38·0%] vs 1215 [45·9%], p<0·0001; β blockers: 1492 [56·6%] vs 1561 [59·0%, p=0·081; α blockers: 140 [5·3%] vs 197 [7·5%, p=0·002] but the use of statins (1683 [63·8%] vs 1761 [63·1%], p=0·588) and anti-platelet agents (2025 [76·8%] vs 2040 [77·0%, p=0·831) were similarly high in the two groups after randomisation. Levels of use of statins and anti-platelet agents remained similarly high in the two groups after randomisation. Vital status was ascertained in 5908 (99·7%) patients at the end of the study. Of the 2122 (80·8%) patients taking telmisartan at the end of the study, 2086 (79·4%) were on the full dose, with only 36 (1·4%) on reduced dose. Non-study angiotensin-receptor blockers were used in 54 (1·8%) patients in the telmisartan group and 84 (2·9%) in the placebo group at 1 year, increasing to 152 (5·8%) and 200 (7·6%) by the end of the study. Other non-study blood-pressure-lowering agents were used more frequently in the placebo group than in the telmisartan group by the end of the study (telmisartan vs placebo—diuretics: 888 [33·7%] vs 1059 [40·0%], p<0·0001; calcium channel blockers: 1003 [38·0%] vs 1215 [45·9%], p<0·0001; β blockers: 1492 [56·6%] vs 1561 [59·0%, p=0·081; α blockers: 140 [5·3%] vs 197 [7·5%, p=0·002] but the use of statins (1683 [63·8%] vs 1761 [63·1%], p=0·588) and anti-platelet agents (2025 [76·8%] vs 2040 [77·0%, p=0·831) were similarly high in the two groups after randomisation. Levels of use of statins and anti-platelet agents remained similarly high in the two groups after randomisation.

Table 2 shows reasons for study drug discontinuation. Fewer patients permanently discontinued treatment with telmisartan than did those receiving placebo. Syncope was rare, despite more minor symptoms of hypotension, such as dizziness, with telmisartan. Renal abnormalities (based on local clinical reports) occurred in 308 (10·4%) patients in the telmisartan group, and 241 (8·1%) in the placebo group, although few permanently discontinued study medications because of these abnormalities (table 2). Doubling of serum creatinine (60 [2·0%] in the telmisartan group vs 42 [1·4%] in the placebo group) or hyperkalaemia (potassium over 5·5 mmol/L, 111 [3·8%] vs 49 [1·6%]) occurred more frequently with telmisartan than with placebo, with no difference in incident renal dialysis (seven [0·24%] vs ten [0·34%]).

Among those with cough as the initial reason for intolerance to ACE inhibitors, the proportion stopping study medication for the same reason was similar and infrequent (14 [0·54%] in the telmisartan group vs 15 [0·57%] in the placebo group). Among those with previous hypotension (n=244), hypotension after randomisation occurred in two (1·5%) patients in the telmisartan group and one (0·9%) in the placebo group; one case of angio-oedema occurred in the placebo group amongst the 75 patients with a history of such disease. There was one case of renal dysfunction in each group in the 58 patients who had reported this as a reason for ACE intolerance.

Mean blood pressure was lower on telmisartan than it was with placebo by 6·2/3·6 mm Hg at 6 weeks, by 4·7/2·4 mm Hg at 1 year, by 4·2/2·3 mm Hg at 2 years, and by 3·2/1·3 mm Hg at study end. The mean weighted difference between groups in blood pressure during the study was 4·0 (SD 1·8)/2·2 (1·2) mm Hg.

Fewer patients in the telmisartan group experienced the primary composite outcome of cardiovascular death, myocardial infarction, stroke, or hospitalisation for heart failure than did patients in the placebo group, although the difference was not statistically significant (465 [15·7%] patients vs 504 [17·0%]; hazard ratio 0·92, 95% CI 0·81–1·05, p=0·216; figure 2) The occurrence of the HOPE study outcome of cardiovascular death, myocardial infarction, or stroke was lower with telmisartan than with placebo (384 [13·0%] patients vs 440 [14·8%], 0·87, 0·76–1·00; p=0·048; figure 3). When we adjusted this p value to account for the 87% overlap between the primary and secondary outcomes and the multiplicity of comparisons, the adjusted p value was 0·068. In the first 18 months there was little benefit, but thereafter there were fewer events on telmisartan (figure 3). Adjustment for the changes in blood pressure did not alter the overall

<table>
<thead>
<tr>
<th>Discontinuation</th>
<th>Telmisartan (n=2954)</th>
<th>Placebo (n=2972)</th>
<th>Relative risk</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of discontinuations (temporary or permanent)</td>
<td>1090 (36·9%)</td>
<td>1143 (38·5%)</td>
<td>0·96</td>
<td>0·215</td>
</tr>
<tr>
<td>Number of patients with permanent discontinuations</td>
<td>619 (21·6%)</td>
<td>705 (23·7%)</td>
<td>0·91</td>
<td>0·055</td>
</tr>
<tr>
<td>Hypotensive symptoms</td>
<td>29 (0·98%)</td>
<td>16 (0·54%)</td>
<td>1·82</td>
<td>0·049</td>
</tr>
<tr>
<td>Syncope</td>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>15 (0·51%)</td>
<td>18 (0·61%)</td>
<td>0·84</td>
<td>0·613</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>7 (0·24%)</td>
<td>2 (0·07%)</td>
<td>3·52</td>
<td>0·094</td>
</tr>
<tr>
<td>Angio-oedema</td>
<td>2 (0·07%)</td>
<td>3 (0·10%)</td>
<td>0·67</td>
<td>0·660</td>
</tr>
<tr>
<td>Renal abnormalities</td>
<td>24 (0·81%)</td>
<td>13 (0·44%)</td>
<td>1·86</td>
<td>0·067</td>
</tr>
</tbody>
</table>

*Most discontinuations were for non-specific reasons, with little difference between the two groups for any specific category.*
results for the primary (hazard ratio 0·92, 95% CI 0·81–1·05) or HOPE secondary outcome (0·87, 0·76–1·00). Subgroup analyses show that the effect of telmisartan on the primary and secondary outcomes was consistent in various subgroups of patients (figure 4).

Of the components of the primary composite outcome, there were fewer myocardial infarctions and strokes in the telmisartan group than in the placebo group, although not significantly so, but the number of cardiovascular deaths and hospitalisations for heart failure were similar between the two groups (table 3). Total mortality was much the same in the two groups (364 [12·3%] deaths vs 349 [11·7%], p=0·491). The combined outcome of macrovascular (cardiovascular death, myocardial infarction, or stroke) and microvascular disease (laser therapy for retinopathy, doubling of creatinine, new macroalbuminuria, or dialysis)—the primary outcome of the ADVANCE study—occurred less frequently with telmisartan than with placebo (523 [17·7%] vs 587 [19·8%], hazard ratio 0·89, 95% CI 0·79–1·00; p=0·049). More patients in the telmisartan group than in the placebo group experienced the composite outcome of macrovascular and microvascular disease plus the development of microalbuminuria (742 [25·1%] vs 861 [29·0%], 0·85, 95% CI 0·77–0·94; p=0·001).

Fewer patients in the telmisartan group had electrocardiographic evidence of left ventricular hypertrophy than did those in the placebo group, and there were fewer patients in the telmisartan group exhibiting signs of new diabetes than in the placebo group, although not significantly so (table 4). Fewer patients were hospitalised for cardiovascular reasons in the telmisartan group than in the placebo group (table 4). There was no difference in the incidence of cancers, either overall or at specific sites (data not shown).

As prespecified, the data from this trial were analysed overall and the events subdivided into those that occurred before and after 6 months of randomisation, based on hypotheses generated from the PROFESSION trial (table 5). Overall, there was a reduction in the relative risk of the primary endpoint when both trials were combined; however, there was no evidence of an effect on this outcome before 6 months. Likewise, the relative risk of the composite of cardiovascular death, myocardial infarction, and stroke was reduced overall, but no benefit was seen in the first 6 months. The effects before and after 6 months of treatment were statistically heterogeneous (p for interaction of <0·001).

**Discussion**

Although fewer patients experienced the primary outcome of cardiovascular death, myocardial infarction, stroke, or hospitalisation for heart failure with telmisartan than with placebo, this result was not statistically significant. However, there was a reduction in the HOPE secondary outcome of cardiovascular death, myocardial infarction, and stroke with telmisartan, compared with placebo.

These results are reinforced by similar trends in the recent PROFESSION study comparing telmisartan with placebo over 2·5 years in patients after a recent stroke. Combined analysis of these two trials demonstrates a significant reduction in the odds of cardiovascular death,
myocardial infarction, and stroke; in both trials, however, there was no effect on hospitalisations for heart failure. When stratified by time, telmisartan had no effect on the composite of cardiovascular death, myocardial infarction, and stroke in the first 6 months in both trials, but there was a clear benefit after 6 months. These analyses suggest that there is a delay of 6–12 months before the benefits of an angiotensin-receptor blocker emerge, and that it could take several years of treatment for the full benefits to manifest.

The lack of effect of telmisartan on hospitalisation for heart failure in both PROFESS and TRANSCEND is unexpected and puzzling, especially since an ACE inhibitor significantly reduced heart failure in the HOPE trial and a combined analysis of the HOPE, Prevention of Events with Angiotensin-Converting-Enzyme (PEACE), and European trial on Reduction Of cardiac events with Perindopril among patients with stable coronary Artery disease (EUROPAT) trials showed significant reductions in hospitalisation for heart failure. The apparent lack of reduction in heart failure with telmisartan in PROFESS trial and TRANSCEND is consistent with the findings in ONTARGET, where the number of hospitalisations for heart failure with ramipril was 354 (4.1%), compared with 394 (4.6%) on telmisartan (risk ratio 1.2, 95% CI 0.97–1.29). This raises the question as to whether telmisartan is less effective than ACE inhibitors in preventing heart failure. However, other angiotensin-receptor blockers have been shown to reduce hospitalisations for heart failure, mainly in patients with low ejection fractions and NYHA Classes II to IV heart failure, in those with severe hypertension and left ventricular hypertrophy, or in hypertensive patients with an angiotensin-receptor blocker compared with amlopidine. By contrast with previous trials of angiotensin-receptor blockers, our patients were not known to have left ventricular systolic dysfunction (heart failure was an exclusion factor), and few had left ventricular hypertrophy at study entry. It is also possible that the risk of any heart failure in the control group in TRANSCEND was unexpectedly low (webtable), which might have contributed to the apparent lack of benefit on these outcomes. For example, the rate of any heart failure in the placebo group of HOPE was 2.40% per year, compared with only 1.49% per year seen here, although this difference was not seen with hospitalisations for heart failure (HOPE placebo 0.84% per year vs TRANSCEND placebo 0.96% per year). In this context, it is worth noting that while ramipril and perindopril reduced the risk of heart failure in the HOPE and PROGRESS trials, which included high-risk patients, the same drugs did not affect heart failure in the DREAM and ADVANCE studies of lower-risk patients. It is possible that when the absolute risk of heart failure is low, ACE inhibitors and angiotensin-receptor blockers might not reduce the incidence of heart failure. The rates of myocardial infarction were also lower in TRANSCEND (placebo event rate of 1.09% per year), compared with 1.32% on telmisartan in PROFESS trial and TRANSCEND is unexpected and puzzling, especially since an ACE inhibitor significantly reduced heart failure in the HOPE.
most previous trials, but in TRANSCEND, as well as in previous trials, the results were consistent in patients receiving or not receiving these drugs. Based on these considerations, it is possible that the TRANSCEND population differs systematically from ONTARGET and previous trials. There were higher rates of diuretic and β-blocker use in the placebo group than in the telmisartan group after randomisation, which would have masked heart failure. Lastly, the play of chance for the apparent lack of reduction in heart failure cannot be excluded.

The results of this trial, and the similarity of effects on myocardial infarction between telmisartan and ramipril (which has been shown to reduce such events) in ONTARGET, should help to dispel concerns that angiotensin-receptor blockers might not reduce myocardial infarction. These findings are consistent with the data on reductions in myocardial infarction with candesartan versus placebo in heart failure. A consistently lower rate of stroke is observed with angiotensin-receptor blockers in TRANSCEND (vs placebo), in ONTARGET (vs an ACE inhibitor), and in the LIFE study (vs β blockers), which is suggestive of a special effect of these drugs on cerebrovascular events, but the evidence is not conclusive.

In TRANSCEND, we enrolled patients intolerant to ACE inhibitors. Despite this, adherence to telmisartan was high and better than with placebo, confirming the tolerability of telmisartan. In fact, even patients who had experienced angio-neurotic oedema and other side-effects while on ACE inhibitors can be given telmisartan. A high proportion of patients in our study were treated with lipid-lowering agents, antiplatelet agents, and other blood-pressure-lowering drugs. Further, more patients in the placebo group received added blood-pressure-lowering drugs than did those in the telmisartan group, which might have minimised the differences in blood pressure seen between the two randomised groups. Consequently, the difference in blood pressure between the two randomised groups was modest. Adjusting for this modest difference in blood pressure did not appreciably change the point estimate for cardiovascular death, myocardial infarction, and stroke seen in both TRANSCEND and PROFESSION, suggesting that a large proportion of the benefits of telmisartan might be independent of blood-pressure lowering. Similar results have been observed in the HOPE study with ramipril and in the LIFE study with losartan.

One can speculate whether more prolonged treatment with telmisartan may have led to a larger benefit. This possibility is supported by analyses of PROFESSION, HOPE, and the LIFE studies, where little or no benefit was seen in the first 6–12 months after randomisation, with benefits perhaps emerging later. A lag before benefits emerge has been seen in several trials of blood-pressure-lowering trials, and also in trials of lipid-lowering agents. This lag might be explained by the time needed to modify the atherothrombotic processes in the arterial wall by the blood-pressure-lowering or lipid-lowering agents, which take months or years to accrue. Further, even in a trial of 5 years of follow-up, the mean duration of treatment to an event (assuming constant hazard) is only 2–5 years. Moreover, with improvements in background therapies such as increased use of statins and blood-pressure-lowering agents, the benefits of adding a further new agent could either be more modest or likely to take longer to emerge. These considerations suggest that trials of new interventions to prevent future vascular events (when added to existing therapies) have

Table 3: Components of the primary outcome

<table>
<thead>
<tr>
<th>Event</th>
<th>Telmisartan</th>
<th>Placebo</th>
<th>Hazard ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular death</td>
<td>227 (7.7%)</td>
<td>223 (7.5%)</td>
<td>1.03 (0.85–1.24)</td>
<td>0.778</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>116 (3.9%)</td>
<td>147 (5.0%)</td>
<td>0.79 (0.62–1.01)</td>
<td>0.059</td>
</tr>
<tr>
<td>Stroke</td>
<td>112 (3.8%)</td>
<td>136 (4.6%)</td>
<td>0.83 (0.64–1.06)</td>
<td>0.136</td>
</tr>
<tr>
<td>Hospitalisation for heart failure</td>
<td>134 (4.5%)</td>
<td>129 (4.3%)</td>
<td>1.05 (0.82–1.34)</td>
<td>0.694</td>
</tr>
</tbody>
</table>

Table 4: Other secondary events and hospitalisations

<table>
<thead>
<tr>
<th>Event</th>
<th>Telmisartan</th>
<th>Placebo</th>
<th>Hazard ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any heart failure</td>
<td>191 (6.5%)</td>
<td>197 (6.6%)</td>
<td>0.98 (0.80–1.19)</td>
<td>0.828</td>
</tr>
<tr>
<td>Revascularisation procedures</td>
<td>349 (11.8%)</td>
<td>390 (13.1%)</td>
<td>0.90 (0.77–1.03)</td>
<td>0.133</td>
</tr>
<tr>
<td>New diabetes or fasting glucose ≥7 mmol/L</td>
<td>359 (20.1%)</td>
<td>393 (21.6%)</td>
<td>0.91 (0.79–1.05)</td>
<td>0.203</td>
</tr>
<tr>
<td>New clinical diagnosis of diabetes</td>
<td>209 (11.0%)</td>
<td>245 (12.8%)</td>
<td>0.85 (0.71–1.02)</td>
<td>0.081</td>
</tr>
<tr>
<td>New atrial fibrillation</td>
<td>182 (6.4%)</td>
<td>180 (6.3%)</td>
<td>1.02 (0.83–1.26)</td>
<td>0.829</td>
</tr>
<tr>
<td>New left ventricular hypertrophy</td>
<td>128 (5.0%)</td>
<td>202 (7.9%)</td>
<td>0.62 (0.50–0.78)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cancers</td>
<td>236 (8.0%)</td>
<td>204 (6.9%)</td>
<td>1.17 (0.97–1.42)</td>
<td>0.094</td>
</tr>
<tr>
<td>Angina with hospitalisation and ECG changes</td>
<td>253 (8.6%)</td>
<td>287 (9.7%)</td>
<td>0.88 (0.74–1.04)</td>
<td>0.135</td>
</tr>
<tr>
<td>Any cardiovascular hospitalisation</td>
<td>894 (30.3%)</td>
<td>980 (33.0%)</td>
<td>0.92 (0.85–0.99)</td>
<td>0.025</td>
</tr>
<tr>
<td>Number of patients hospitalised</td>
<td>1472 (50.0%)</td>
<td>1526 (51.4%)</td>
<td>0.97 (0.93–1.02)</td>
<td>0.300</td>
</tr>
<tr>
<td>Total mortality</td>
<td>364 (12.3%)</td>
<td>349 (11.7%)</td>
<td>1.05 (0.91–1.22)</td>
<td>0.491</td>
</tr>
</tbody>
</table>

Table 5: Combined analyses of the results of TRANSCEND and PROFESSION trials comparing telmisartan with placebo
to seek modest benefits (eg, relative risks of 10–15%) and be more prolonged to ensure that the full benefits of such interventions become evident. Further, the continuing benefits seen after stopping randomised therapy for several years after completion of some trials of lipid lowering\textsuperscript{32,33} or ACE inhibitors\textsuperscript{34} suggest that once the biological processes in the vessel wall are favourably modified, the benefits might continue to accrue.

The effect of telmisartan on the incidence of diabetes seen here seems to be smaller than in previous trials of ACE inhibitors or angiotensin-receptor blockers.\textsuperscript{35} However, in some previous trials, diabetes was not a prespecified hypothesis,\textsuperscript{36} the population included those with intense activation of the RAAS (renin-angiotensin-aldosterone system; eg, patients with heart failure),\textsuperscript{37} the comparator was an agent such as a ß blocker or a diuretic,\textsuperscript{38,39} and in many studies glucose was not systematically measured, as the diagnosis was made solely on clinical grounds. In the only trial to prospectively assess this question (DREAM),\textsuperscript{40} a 9% non-significant benefit in preventing diabetes was observed with ramipril, which is consistent with our results. Although the effect of telmisartan on the primary outcome in a population of patients intolerant to ACE inhibitors was not statistically significant, and interpretation of differences in secondary outcomes should be undertaken with caution, the HOPE outcome was reduced with telmisartan compared with placebo. Further, the ONTARGET trial shows non-inferiority of telmisartan versus ramipril, and there was a trend towards fewer events in the PROFESS trial. A prespecified analysis combining the results of TRANSCEND and PROFESS on this outcome is statistically significant, especially with more prolonged treatment (table 5). Further, there was a reduction in the combined outcome of microvascular and macrovascular events and in cardiovascular hospitalisations (as used in ADVANCE)—again suggesting clinical benefit. These data suggest that telmisartan confers a modest added benefit when added to other proven therapies. In view of the drug’s tolerability and effects on cardiovascular endpoints, telmisartan could be regarded as a potential treatment for patients with vascular disease or high-risk diabetes, if they are unable to tolerate an ACE inhibitor.

**Contributors**

The study was designed and conducted by the steering committee. SY and KT wrote the initial drafts of the manuscript, with detailed comments on several versions from the writing group, and additional comments from the members of the steering committee. The writing group has full access to the data and vouches for the accuracy of the data and analyses.

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Conflict of interest statement

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