Original Article

ARE ACE-INHIBITORS OR ARB'S STILL NEEDED FOR CARDIOVASCULAR PREVENTION IN HIGH RISK PATIENTS? INSIGHTS FROM PROFESS AND TRANSCEND

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ABSTRACT

The HOPE and EUROPA clinical studies have shown that treatment with the angiotensin-converting enzyme (ACE) inhibitors, ramipril and perindopril, may reduce the occurrence of major cardiovascular events in patients with proven atherosclerotic disease.

The recently published results of the PRoFESS and TRANSCEND trials completed the much needed information concerning the use of an angiotensin receptor blocker for patients at high risk of cardiovascular events. PRoFESS compared a therapy of telmisartan 80 mg daily with placebo in patients with a recent ischemic stroke. The difference in the primary outcome of first recurrent stroke was not statistically significant between telmisartan and placebo. The secondary outcome of major cardiovascular events showed a relative risk reduction (RRR) of 7% in favour of telmisartan. This tended to be significant (p= 0.06) despite a rather short follow-up period of only 28 months. In TRANSCEND 5,926 patients at high risk for cardiovascular events were randomized to a treatment with telmisartan 80 mg daily or placebo for a mean duration of follow-up of 56 months. The primary composite outcome of cardiovascular death, myocardial infarction, stroke or hospitalization for heart failure showed a non-significant 8% RRR in favour of the telmisartan treated patients. The main secondary outcome of cardiovascular death and myocardial infarction or stroke as used in the HOPE trial **showed a non-significant** RRR of 13% in favour of telmisartan treated patients (p= 0,068 adjusted for multiplicity of comparisons). In comparing the Kaplan-Meier curves for the endpoint of major cardiovascular events used in HOPE, EUROPA, TRANSCEND and PRoFESS, the trends are similar. Results of most of the recently published trials have been neutral. This could partly be explained by major

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improvements in the optimal background therapy of the patients included. Nevertheless, the results of PRoFESS and TRANSCEND do not contradict the results from previous studies with the ACE inhibitors ramipril and perindopril and the ARB telmisartan.

INTRODUCTION

Angiotensine II has a prominent role in the pathogenesis and further evolution of the atherosclerotic disease (1,2). It has been shown in 2 large clinical trials that angiotensine-converting enzyme (ACE) inhibitors can significantly prevent serious cardiovascular events in patients at high risk. The "Heart Outcome Prevention Evaluation" (HOPE) study (3) randomized 9297 high risk patients with age > 55 years and proven atherosclerotic disease (coronary, cerebrovascular or peripheral) or diabetes mellitus with an additional risk factor (arterial hypertension, hypercholesterolemia, low HDL-cholesterol, smoking or micro-albuminuria) to a treatment with ramipril 10 mg per day or placebo for a mean follow-up of 4,5 years. The primary composite endpoint was myocardial infarction (MI), stroke or cardiovascular death. In the group of patients treated with ramipril, a relative risk reduction (RRR) of 22% of the primary endpoint was noticed compared to the placebo treatment ($p < 0,001$) with in addition a highly significant reduction in several secondary endpoints. In the "European trial on reduction of cardiac events with perindopril and stable coronary artery disease" (EUROPA) (4), 13655 patients, age > 55 years and proven coronary artery disease were randomised to a treatment with perindopril 8 mg per day or placebo. After a mean follow up of 4,2 years, a RRR of the composite primary endpoint (cardiovascular death, MI or cardiac arrest) of 20% ($p= 0,0003$) was seen in favor of the patients treated with perindopril. Questions at that time were whether a treatment with an angiotensin-receptor blocker (ARB) could be as effective in the prevention of cardiovascular complications for patients at high risk and furthermore of the combination of an ACE inhibitor with an ARB could not be even more effective than single drug therapy with an ACE inhibitor. The answers on this questions were evaluated in the ONTARGET study program.

The ONTARGET programme (5) consisted of two parallel trials: the "ONgoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial" (ONTARGET) and the "Telmisartan Randomized AssesmeNt Study in aCE iNtolerant subjects with cardiovascular Disease" (TRANSCEND).

ONTARGET (6) compared an angiotensin converting enzyme inhibitor (ACEi) versus an angiotensin receptor blocker (ARB) versus a combination of both in high risk individuals. The primary objectives of ONTARGET were to determine if the combination of telmisartan 80 mg daily and ramipril 10 mg daily is more effective in reducing the composite outcome of cardiovascular (CV) deaths, myocardial infarction (MI), stroke or hospitalization for congestive heart failure (CHF) than ramipril 10 mg alone and whether telmisartan 80 mg daily alone is at least as effective (i.e. "not inferior") as ramipril 10 mg alone daily. The primary objective of TRANSCEND (7) was to determine if treatment with telmisartan 80 mg daily is superior to placebo in patients who were intolerant to ACE-inhibitors. In both trials patients were included with coronary artery, peripheral vascular or cerebrovascular disease or high risk diabetes mellitus with end organ damage. Patients with known intolerance to ACE inhibitors were randomized to telmisartan or placebo in the TRANSCEND trial. The answers were clear: telmisartan 80 mg can be considered equivalent to ramipril 10 mg for the protection against cardiovascular death, MI, stroke and hospitalization for congestive heart failure. The combination therapy did not reduce the risk of cardiovascular death, MI, stroke and hospitalization for congestive heart failure to a greater extent compared to ramipril alone. On the contrary, the combination therapy was associated with a higher rate of adverse events and a trend towards a higher mortality.

The "Telmisartan to Prevent Recurrent Stroke and Cardiovascular Events (PRoFESS)" trial had as primary objective to evaluate whether therapy with the ARB telmisartan given at a dose of 80 mg per day could reduce the risk of stroke when initiated within 3 months after stroke and continued for 2.5 years. A prespecified analysis combining the results of TRANSCEND and PRoFESS was performed as well (7).

THE PRoFESS trial

After a stroke, lowering blood pressure with combination of an ACEi and a thiazide type diuretic reduced rates of recurrent stroke in the Perindopril PROtection

aGainst RecurrEnt Stroke Study (PROGRESS). In PROGRESS (9), 71% of the patients had an ischemic stroke and were enrolled at a median of 8 months after the qualifying event. The aim of the PRoFESS study was to evaluate whether therapy with the ARB telmisartan given at the dose of 80 mg per day could reduce the risk of stroke when initiated within 3 months after an ischemic stroke and continued for 2.5 years. A total of 20,332 patients were enrolled in the PRoFESS trial between September 11, 2003 and July 14, 2006. Of these patients, 10,146 were assigned to receive telmisartan and 10,186 to receive placebo. The median time from the qualifying stroke to randomization was 15 days and 39.8 % of the patients were randomized within 10 days after the event. The mean blood pressure at entry was 144.1 mmHg systolic and 83.8 mmHg diastolic. The most important baseline characteristics of the patients are given in table 1. The primary outcome was recurrent stroke of any type. The two secondary outcomes were major cardiovascular events (death from cardiovascular causes, MI, recurrent stroke or new or *worsening* CHF) and new onset diabetes.

MAIN RESULTS OF PRoFESS

The mean duration of follow up was 30 months. The average between group difference in systolic and diastolic blood pressure was 3.8/2 mmHg throughout the study. The primary outcome of first recurrent stroke occurred in 880 patients (8.7%) in the telmisartan group, compared with 934 patients (9.2%) in the placebo group (hazard ratio 0.95; p= 0.23) (Table 2). The number of patients with a major cardiovascular event was 1,367 (13.5%) in the telmisartan group, as compared with 1,463 (14.4%) in the placebo group (hazard ratio 0.93; p= 0.067) (8). The number of patients

Table 1. Baseline characteristics of the patients in PRoFESS

Variable	Telmisartan (N= 10.146)	Placebo (N= 10.186)
Age – yr mean (SD)	66.1 ± 8.6	66.2 ± 8.6
Blood pressure – mmHg mean (SD)	144.1 ± 16.4 / 83.8 ± 10.5	144.2 ± 16.7 /83.8 ± 10.6
Female gender – n (%)	3.619 (35.7)	3.691 (36.2)
Clinical history – n (%)		
Previous stroke or TIA	2.486 (24.5)	2.511 (24.7)
Atherosclerotic disease (p= 0.05)	1.898 (18.7)	2.053 (20.2)
Atrial fibrillation	266 (2.6)	274 (2.7)
Hypertension	7.510 (74.0)	7.538 (74.0)
Diabetes mellitus	2.840 (28.0)	2.903 (28.5)
Hyperlipidemia	4.735 (46.7)	4.758 (46.7)
Use of medication at baseline – n (%)		
Statin	4.742 (46.7)	4.872 (47.8)
ACE inhibitor	3.737 (36.8)	3.782 (37.1)
Diuretic	2.093 (20.6)	2.168 (21.3)
Calcium channel blocker	2.487 (24.5)	2.473 (24.3)
Beta blocker	2.096 (20.7)	2.135 (21.0)

Adapted from ref 4

Table 2. Effect of telmisartan on primary and secondary outcomes in PRoFESS

Outcome	Telmisartan (N= 10.146) n (%)	Placebo (N= 10.186) n (%)	Hazard Ratio (95% CI)*	P Value
Primary				
Recurrent stroke †	880 (8.7)	934 (9.2)	0.95 (0.86-1.04)	0.23
Secondary				
Death from cardiovasc. causes, recurrent stroke, MI, or new of worsening HF	1.367 (13.5)	1.463 (14.4)	0.93 (0.86-1.01)	0.067
Death from cardiovascular causes ‡	223 (2.2)	263 (2.6)		
Recurrent stroke ‡	855 (8.4)	914 (9.0)		
Myocardial infarction ‡	168 (1.7)	169 (1.7)		
New or worsening heart failure ‡	121 (1.2)	117 (1.1)		
New onset diabetes	125 (1.2)	151 (1.5)	0.82 (0.65-1.04)	0.10

* Hazard ratios are for patients in the telmisartan group, as compared with the placebo group.
† Numbers are based on the incidence of the first recurrent stroke.
‡ This event was the first that occurred in the composite outcome.
# Ref 3.

Adapted from ref 4

Table 3: Baseline characteristics of the patients in TRANSCEND and HOPE

Variable	TRANSCEND Telmisartan (N= 2.954)	TRANSCEND Placebo (N= 2.972)	HOPE Ramipril (N= 4645)
Age (years)	66.9 (7.3)	66.9 (7.4)	66 (7)
Blood pressure (mmHg)	140.7 / 81.8	141.3 / 82.0	139 / 79
Female gender - n (%)	1.280 (43.3%)	1.267 (42.6%)	1.279 (27.5%)
Coronary artery disease	2.211 (74.8%)	2.207 (74.3%)	3.691 (79.5%)
Myocardial infarction	1.381 (46.8%)	1.360 (45.8%)	2.410 (51.9%)
Angina pectoris	1.412 (47.8%)	1.412 (47.5%)	2.544 (54.8%)
Stroke or transient ischemic attack	648 (21.9%)	654 (22.0%)	500 (10.8%)
Peripheral artery disease	349 (11.8%)	323 (10.9%)	1.966 (42.3%)
Hypertension	2.259 (76.5%)	2.269 (76.3%)	2.212 (47.6%)
Diabetes	1.059 (35.8%)	1.059 (35.6%)	1.808 (38.9%)
Medications			
Statin	1.645 (55.7%)	1.627 (54.7%)	1.318 (28.4%)
Betablocker	1.753 (59.3%)	1.700 (57.2%)	1.820 (39.2%)
Antiplatelet agent	2.356 (79.8%)	2.349 (79.0%)	3.497 (75.3%)
Calcium channel blocker	1.179 (39.9%)	1.202 (40.4%)	2.152 (46.3%)

Data are mean (SD) or n (%).

Adapted from ref 3 and 12

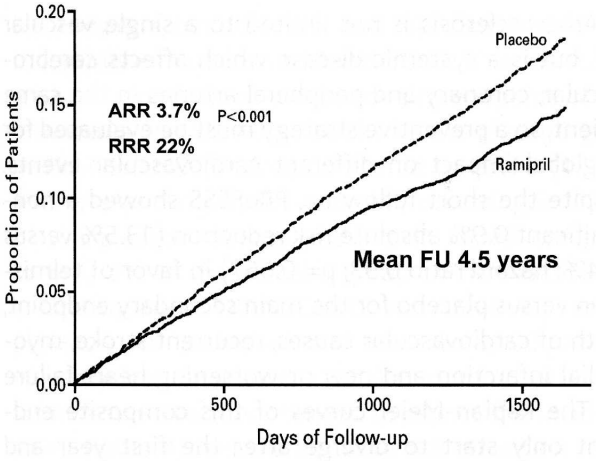
who had new onset diabetes after randomization was 125 (1.2%) in the telmisartan group, as compared with 151 (1.5%) in the placebo group (hazard ratio 0.82; p= 0.10) (table 2). Adverse events leading to discontinuation of the study drug were 14.3% in the telmisartan group versus 11.1% in the placebo group ($p < 0.001$). Hypotensive symptoms (3.9% versus 1.8%; $p < 0.001$) and syncope (0.2 versus 0.1%; p= 0.004) led to study discontinuation significantly more often in the telmisartan group than in the placebo group.

THE TRANSCEND TRIAL

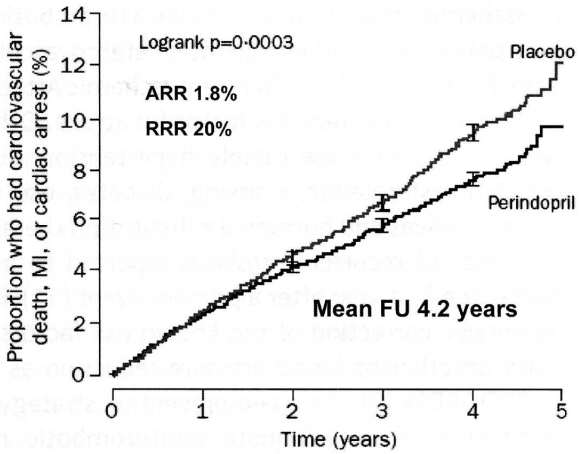
A total of 5,926 patients were randomized to receive telmisartan 80 mg/day (n= 2,954) or placebo (n= 2,972). The mean age of the patients was 66.9 years and the mean blood pressure 141/81 mmHg. The most important baseline characteristics of the patients are given in table 3. The primary outcome was the composite of cardiovascular death, MI, stroke, hospitalization for heart failure. One of the secondary outcomes was the composite of cardiovascular death, MI or stroke (the primary outcome of HOPE). Other interesting secondary outcomes were new clinical diagnosis of diabetes and new atrial fibrillation. Before the completion of PRoFESS and TRANSCEND, it was specified that a combined analysis of the data from the 2 trials would be done.

MAIN RESULTS OF TRANSCEND

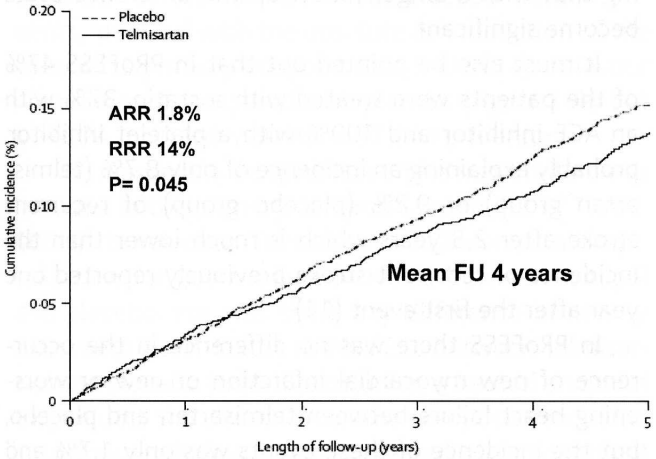
The mean duration of follow up was 56 months. The mean weighted difference between groups in blood pressure during the study was 4.0/2.2 mmHg. The primary composite outcome of cardiovascular death, MI, stroke, hospitalization for heart failure occurred in 465 patients (15.7%) in the telmisartan group, compared with 504 patients (17%) in the placebo group (hazard ratio 0.92; p= 0.216). The occurrence of the HOPE study outcome of cardiovascular death, MI or stroke was significantly lower with telmisartan (384; 13%) than with placebo (440; 14.8%; hazard ratio 0.87; p= 0.048 unadjusted; p= 0.068 after adjustment for multiplicity of comparisons). Of the components of the primary composite outcome there tended to be fewer myocardial infarctions or strokes in the telmisartan group compared to the placebo group. Cardiovascular deaths and hospitalization for heart failure were not significantly different (table 4). There was a tendency to fewer episodes of newly diagnosed diabetes mellitus, but no difference in the occurrence of new onset atrial fibrillation (table 4) The prespecified combined analysis of the results of TRANSCEND and PRoFESS comparing telmisartan with placebo, showed a reduction in the relative risk of the primary endpoint of cardiovascular death, MI, and stroke, with (p= 0.026) or without (p= 0.013) the inclusion of hospitalization for heart failure (7).



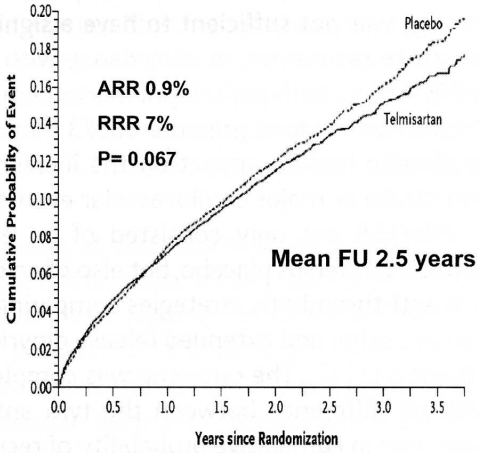
Kaplan Meier curves of the composite endpoint of CV death, MI or stroke in HOPE (A).



Kaplan Meier curves of the composite endpoint of CV death, MI or cardiac arrest in EUROPA (B) (11).



Kaplan Meier curves of the composite endpoint of CV death, MI or stroke in TRANSCEND (C) (3).



Kaplan Meier curves of the composite endpoint of CV death, MI, troke or hospitalization for HF in PROFESS (D) (4).

DISCUSSION

ONTARGET was a landmark trial because of the size of the studied patient population, the number of observed events, the quality of the data and the length of follow up. It unequivocally answered the two important questions it was designed for (10).

PRoFESS and TRANSCEND are as important to complete the picture of the position of ARB's (telmisartan) for prevention in high risk cardiovascular patients with a recent ischemic stroke or a history of atherosclerotic disease or diabetes with end organ damage. At first glance, the results do not seem to be straightforward, partially due to flaws in the design of the two trials. A clarifying interpretation seems warranted.

Table 4: Effect of telmisartan on primary and selected secondary outcomes in TRANSCEND

	Telmisartan	Placebo	Hazard ratio (95% CI)	p value
Cardiovascular death	227 (7.7%)	223 (7.5%)	1.03 (0.85-1.24)	0.778
Myocardial infarction	116 (3.9%)	147 (5.0%)	0.79 (0.62-1.01)	0.059
Stroke	112 (3.8%)	136 (4.6%)	0.83 (0.64-1.06)	0.136
Hospitalization for HF	134 (4.5%)	129 (4.3%)	1.05 (0.82-1.34)	0.694
New clinical diagnosis of diabetes	209 (11.0%)	245 (12.8%)	0.85 (0.71-1.02)	0.081
New atrial fibrillation	182 (6.4%)	180 (6.3%)	1.02 (0.83-1.26)	0.829

Adapted from ref 3

Ischemic stroke is in most cases a thrombotic event in a patient with atherosclerotic cerebrovascular disease. Previous stroke or Transient Ischemic Attack (TIA) is the most important risk factor for stroke. Other risk factors for stroke are mainly hypertension, but also hypercholesterolemia, smoking, diabetes, use of oral contraceptives and hormonal substitution therapy. The incidence of recurrent stroke is reported to be 12% during the first year after a primary event (11). Besides aggressive correction of the known risk factors, especially an efficient blood pressure reduction as shown in PROGRESS (9), the main preventive strategy is the institution of an adequate antithrombotic regime. The difference in blood pressure in PRoFESS between telmisartan and placebo treated patients (3.8 / 2.0 mmHg) was not sufficient to have a significant effect on stroke recurrence, in accordance with the findings in PROGRESS with perindopril monotherapy (9) where a reduction in blood pressure of 5/3 mmHg compared to placebo had no impact on the incidence of recurrent stroke or major cardiovascular events.

PRoFESS not only consisted of an evaluation of telmisartan versus placebo, but also of an evaluation of two anti-thrombotic strategies comparing a combination of aspirin and extended release dipyridamole with clopidogrel (12). The outcome was completely neutral with no difference between the two antithrombotic strategies in cumulative probability of recurrent stroke or cumulative probability of stroke, MI or death from vascular causes.

The design of PRoFESS clearly implicates that the main purpose of the study was to address the difference between the two anti-thrombotic treatments. The mean follow up in PRoFESS was only 2.5 years. The impact of an angiotensin receptor blocker on atherosclerotic / atherothrombotic disease is not on the atherothrombotic part which can be evaluated rapidly but thought to be an effect on the atherosclerotic aspect consisting mainly of stabilization of the plaque and improvement of endothelial function (1,2).

The combined analysis of Profess and Transcend demonstrates a significant reduction in the odds of cardiovascular death, myocardial infarction and stroke. When stratified by time, telmisartan had no effect on this composite outcome in the first 6 months in both trials but there was a clear benefit after 6 months. These analysis suggest that there is a delay of 6-12 months before the benefits of an ARB emerge and that it could take several years of treatment for the full benefits to manifest (3, 4), as has been seen in several trials of blood pressure or lipid lowering agents as well (13,14).

Atherosclerosis is not limited to a single vascular bed, but is a systemic disease which affects cerebrovascular, coronary and peripheral arteries in the same patient, so a preventive strategy must be evaluated for its global impact on different cardiovascular events. Despite the short follow up, PRoFESS showed a non-significant 0.9% absolute risk reduction (13.5% versus 14.4%; hazard ratio 0.93; p= 0.067) in favor of telmisartan versus placebo for the main secondary endpoint, death of cardiovascular causes, recurrent stroke, myocardial infarction and new or worsening heart failure (8). The Kaplan-Meier curves of this composite endpoint only start to diverge after the first year and continue to diverge further on (figure 1-D), suggesting that with a longer follow up the difference could become significant.

It must also be pointed out that in PRoFESS 47% of the patients were treated with a statin, 37% with an ACE-inhibitor and 100% with a platelet inhibitor, probably explaining an incidence of only 8.7% (telmisartan group) or 9.2% (placebo group) of recurrent stroke after 2.5 years which is much lower than the incidence of recurrent stroke previously reported one year after the first event (11).

In PRoFESS there was no difference in the occurrence of new myocardial infarction or new or worsening heart failure between telmisartan and placebo, but the incidence of these events was only 1.7% and 1.2%. The non-significant trend towards a lower rate of new onset diabetes associated with telmisartan did not confirm but was in accordance with the results of several previous trials that have suggested that ACE-inhibitors and ARB's can reduce the risk of development of diabetes (15). Furthermore the incidence of new onset diabetes was very low in the two treatment groups (1,2% and 1,5%), but the Kaplan-Meier curves for the cumulative probability of new onset diabetes continuously diverged in favour of telmisartan, again suggesting that a longer duration of follow up was needed. PRoFESS was clearly underpowered to detect significant differences in these secondary endpoints over this relatively short period of follow up.

Driven by the spectacular results of HOPE (3), the investigators of TRANSCEND estimated that an overall sample size of 6,000 patients was expected to be 94% powered to find a 19% relative risk reduction in favour of telmisartan compared to placebo (5). This was a higher power and more robust effect size than in HOPE. Compared to the background treatment in HOPE, the use of other lifesaving drugs such as plate-

let inhibitors, beta blockers and especially statins was much more frequent in TRANSCEND. This resulted in a lower incidence of the composite endpoint of cardiovascular death, MI or stroke in the placebo group in TRANSCEND (14.8%) compared to HOPE (17.8%). This is especially striking for MI, occurring in 12.3% of the placebo treated patients in HOPE compared to only 5% in the placebo group of TRANSCEND. As a consequence, TRANSCEND was relatively underpowered with an inclusion of not even 6,000 patients. Nevertheless, despite the smaller number of events, telmisartan treatment tended to reduce the incidence of MI (table 4) and the absolute risk reduction of the composite outcome CV death, MI and stroke was 1.8% in favour of telmisartan versus placebo treated patients, identical with the absolute risk reduction of the composite primary endpoint in EUROPA (4), in favour of perindopril compared with placebo (figure 1-B), but EUROPA included more than 12,000 patients.

The reason why hospitalization for heart failure was included in the primary composite endpoint of TRANSCEND is not clear. There was no difference in hospitalization for heart failure in HOPE between ramipril and placebo, nor was there any difference in new or worsening heart failure in PRoFESS between telmisartan and placebo (table 5). Including a neutral endpoint only dilutes the effect size on the composite endpoint.

Although it has been suggested that treatment with ACE-inhibitors or ARB's might be useful for the prevention of new onset diabetes or atrial fibrillation (15,16), the results of TRANSCEND do not seem to confirm these expectations, although there is a trend to fewer episodes of new clinical diagnosis of diabetes when the patients were treated with telmisartan compared to placebo, as was the case in PRoFESS. It must be noted that in a posthoc analysis of HOPE (17) there was no difference in the occurrence of atrial fibrillation between patients treated with ramipril versus placebo. After the spectacular results obtained with ramipril in the HOPE trial, the results of TRANSCEND may seem disappointing, especially after the finding that treatment of high risk cardiovascular patients with telmisartan was equivalent to a treatment with ramipril. A possible explanation is a significant difference in baseline medication.

As can be seen from the baseline data of the patients in TRANSCEND and HOPE, the treatment of patients at high cardiovascular risk has much improved over time, resulting in a smaller number of events despite a higher risk profile with more women and more patients with a history of arterial hypertension in TRANSCEND (table 3). In a 10 year survey conducted in New Jersey and Pennsylvania there was a 3% reduction in mortality per year over a 10 year period from 1995 to 2004 in elderly patients after MI (18), fully explained by a more widespread use of the combination of platelet inhibitors, beta blockers, ACE-inhibitors or ARB's and statins. This means that the benefit of adding a new drug to the background therapy of well treated patients can only be expected to be moderate at the most (19). This may explain the neutral results of many recent clinical trials in cardiovascular disease.

When looking at the results of an individual trial, we should not isolate these results, but compare them with what has been reported in other clinical trials with similar patients and the same or similar drugs.

If one compares the Kaplan-Meier curves of major cardiovascular events of active treatment with ramipril, perindopril or telmisartan versus placebo in HOPE, EUROPA, TRANSCEND and PRoFESS (figure 1), it is clear that the results are in complete accordance taking into account the insufficient number of patients included in TRANSCEND and the insufficient duration of follow up in PRoFESS.

LIMITATIONS OF THE MANUSCRIPT

In order to compare as much as possible similar endpoints of the different clinical studies, for HOPE and EUROPA the primary composite endpoints were used, for TRANSCEND and PRoFESS, so we used a secondary endpoint identical or as similar as possible to

Table 5: Heart failure in HOPE, PRoFESS and TRANSCEND

	N patients (% of patients)		Hazard ratio	P value
	Active	*Placebo*		
HOPE†	141 (3.0)	160 (3.4)	0.88 (0.70 – 1.10)	0.25
PRoFESS‡	121 (1.0)	117 (1.1)		
TRANSCEND†	134 (4.5)	129 (4.3)	1.05 (0.82 – 1.34)	0.694

† Hospitalizations for heart failure
‡ New or worsening heart failure
Adapted from ref. 12,4 and 3.

the primary endpoint in HOPE. Using secondary endpoints may of course weaken the conclusions but especially in the case of PROFESS with as primary endpoint recurrent stroke, a comparison would not have been possible.

Since ACE-inhibitors and ARB's are blood pressure lowering drugs, part of their effect on cardiovascular prevention can probably be explained by differences in blood pressure between active drug and placebo throughout the studies. Nevertheless, adjusting for the modest difference in blood pressure did not appreciably change the point estimate for cardiovascular death, myocardial infarction and stroke seen in both TRANSCEND and PRoFESS, suggesting that a large proportion of the benefits of telmisartan might be independent of blood pressure lowering (7). Similar results have been observed in the HOPE study with ramipril (3).

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