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# Impact of telmisartan on cardiovascular outcome in hypertensive patients at high risk: a Telmisartan Randomised Assessment Study in ACE iNtolerant subjects with cardiovascular Disease subanalysis

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See editorial comment on page 1201

**Background:** In the Telmisartan Randomised Assessment Study in ACE iNtolerant subjects with cardiovascular Disease, all patients were at high cardiovascular risk, and a substantial proportion were hypertensive. We performed a post-hoc analysis to explore the hypothesis that telmisartan has a differential action in hypertensive vs. nonhypertensive patients.

**Methods:** The primary four-fold endpoint (composite of cardiovascular death, myocardial infarction (MI), stroke, or hospitalization for heart failure), the secondary three-fold endpoint (cardiovascular death, MI, and stroke), the individual components, new onset of left ventricular hypertrophy (LVH), and new onset of albuminuria were analyzed.

**Results:** There was no evidence for a significantly differential treatment effect of telmisartan in hypertensive and nonhypertensive patients for any endpoints, although the occurrence of the secondary three-fold endpoint was significantly lower in the telmisartan group (13.0%) compared with placebo (15.0%,  $P < 0.05$ ) only in hypertensive patients. Moreover, data from this post-hoc analysis suggest that MI may be less frequent in hypertensive patients treated with telmisartan (3.8 vs. 5.1%;  $P < 0.05$ ). Telmisartan may also reduce new onset of LVH (nonhypertensive patients  $P < 0.05$ ; hypertensive patients  $P < 0.001$ ) in both subgroups, and new onset of microalbuminuria and macroalbuminuria in hypertensive patients ( $P < 0.001$  and  $P < 0.01$ , respectively). The effect of telmisartan in hypertensive and nonhypertensive patients at high cardiovascular risk was not different. This post-hoc analysis suggests that MI may be further reduced by telmisartan in hypertensive patients. Further investigations are needed to study the hypotheses raised by this explanatory analysis.

**Keywords:** angiotensin receptor blocker, hypertension, myocardial infarction, telmisartan

**Abbreviations:** ACE, angiotensin converting enzyme; ARB, AT<sub>1</sub> receptor blocker; ASA, acetylsalicylic acid; CAD, coronary artery disease; CCB, calcium channel blocker; LVH, left ventricular hypertrophy; MI, myocardial infarction;

TIA, transient ischemic attack; UACR, urinary albumin-creatinine ratio

## INTRODUCTION

The Telmisartan Randomised Assessment Study in ACE iNtolerant subjects with cardiovascular Disease (TRANSCEND) investigated whether long-term treatment with the AT<sub>1</sub> receptor blocker (ARB), telmisartan, in addition to other usual therapies, could reduce cardiovascular death, myocardial infarction (MI), stroke, or hospitalization for heart failure in patients at high cardiovascular risk or high-risk diabetes but without heart failure, who were intolerant of angiotensin-converting enzyme (ACE) inhibitors [1]. In the overall patient population, telmisartan did not significantly modify the primary outcome, which included hospitalizations for heart failure, but reduced the risk of the composite outcome of cardiovascular death, MI, or stroke.

Among the patients enrolled in the trial, 86% were hypertensive. Hypertension is well known to represent a major cardiovascular risk factor [2]. In order to evaluate whether telmisartan had a differential effect in subgroups of hypertensive and nonhypertensive patients, we performed a post-hoc analysis of the TRANSCEND trial in hypertensive vs. nonhypertensive individuals. Hypertension was defined

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as patients with a medical history of hypertension or with a sitting SBP at least 140 mmHg or a DBP at least 90 mmHg at the start of the run-in.

## METHODS

### Study population

The design of TRANSCEND study has been previously described [1,3]. This trial is registered with ClinicalTrials.gov, number NCT00153101. Briefly, patients aged at least 55 years intolerant to ACE inhibitors were enrolled if they had established CAD (coronary artery disease), peripheral vascular or cerebrovascular disease, or diabetes with end-organ damage. After a 3-week run-in period, participants were randomized to telmisartan 80 mg or placebo. Participants were followed-up after 6 weeks and then every 6 months, thereafter for a median of 56 months. In this post-hoc analysis, subgroups of hypertensive and nonhypertensive patients were defined according to the following definition: hypertensive patients were defined as patients with a medical history of hypertension or with a sitting SBP at least 140 mmHg or a DBP at least 90 mmHg at the start of the run-in. In the nonhypertensive subgroup, many patients received, however, blood pressure (BP)-lowering drugs at baseline. Therefore, the nonhypertensive groups may also include hypertensive patients with controlled BP.

### Statistical analyses

Baseline data were compared for differences between hypertensive individuals and nonhypertensive individuals by means of the  $\chi^2$ - and *t*-test. For all cardiovascular endpoints, time to first event was analyzed using a Cox model, including the subgroup information (hypertensive/nonhypertensive) and the respective interaction with treatment. Adjustment was made for age, sex, BMI, race, smoking, alcohol consumption, reason for study entry [CAD, peripheral arterial disease, stroke, transient ischemic attack (TIA), and high-risk diabetes], medical history (previous MI, previous stroke, and presence of diabetes), and concomitant medication [acetylsalicylic acid,  $\beta$ -blocker, diuretics, calcium channel blocker (CCBs), and statins] at baseline.

As in the original publication, the events were subdivided into those that occurred before and after 6 months of randomization, based on a hypothesis from the Prevention Regimen for Effectively Avoiding Second Strokes Trial (PROFESS) [4]. An additional analysis was conducted to test if the effect of telmisartan in hypertensive individuals was different in the first 6 months compared with the later time period.

New onset of left ventricular hypertrophy (LVH) was diagnosed based on electrocardiography, which was routinely done during the study. A urinary albumin-creatinine ratio (UACR) at least 30 mg/g creatinine was defined as microalbuminuria and a value of at least 300 mg/g creatinine as macroalbuminuria.

Because a majority of the population was hypertensive, the number of patients in the two subgroups was unbalanced. As a consequence, statistical analyses may lack the statistical power to show differences between subgroups.

All analyses were done with SAS version 9.2 (SAS Institute Inc, Cary, North Carolina, USA). All tests were

two-tailed, *P* values < 0.05 were considered significant. For interaction tests, due to the lack of power of interaction tests, a threshold of 0.2 was used to decide on relevant heterogeneity of treatment effects between subgroups. No corrections were made for multiple testing.

## RESULTS

This post-hoc analysis was performed to explore the hypothesis that telmisartan has a differential action in patients at high cardiovascular risk with or without hypertension. The following results are thus all observational and should not be considered as conclusive.

### Patients characteristics at baseline

Hypertensive and nonhypertensive patients differed in most of their baseline conditions. Hypertensive patients were older, more likely women, and had a higher BMI compared with nonhypertensive patients (Table 1). The mean sitting BP (SBP/DBP) in hypertensive patients was 144/83 (SD 16/10) mmHg compared with nonhypertensive patients with 124/74 (SD 10/8) mmHg ( $P < 0.0001$ ). Pulse pressure and resting heart rate were significantly higher in the hypertensive patient population. UACR was higher in hypertensive patients ( $P < 0.0001$ ). Previous MIs were more frequent in the nonhypertensive subgroup, whereas stroke/TIA were more frequent in the hypertensive subgroup. Of the hypertensive patients, 4528 (88.9%) had a history of hypertension, whereas 570 patients (11.1%) had no documented history of hypertension despite elevated BP levels at study entry. Hypertension and the concomitant clinical history were also reflected by different medications at baseline. BP-lowering drugs were more often present in medications of hypertensive patients, whereas in nonhypertensive patients, aspirin and statins were used more frequently, probably due to the higher rate of previous MI in this group. However, even in the so-called nonhypertensive subgroup, many patients also received BP-lowering drugs ( $\beta$ -blockers, diuretics, and CCBs mostly).

### Impact of telmisartan on SBP

SBPs were lower throughout the study in telmisartan-treated patients compared with patients treated with placebo (standard treatment without an ARB) in hypertensive (mean SBP during the period of follow-up  $\pm$  SD: telmisartan  $136 \pm 2$  mmHg; placebo  $140 \pm 2$  mmHg,  $P < 0.0001$ ) as well as in nonhypertensive patients (telmisartan  $123 \pm 2$  mmHg; placebo  $129 \pm 3$  mmHg,  $P < 0.0001$ ). In the hypertensive subgroup, the mean postrandomization SBP was reduced (from baseline) by 7.4 mmHg in the telmisartan group compared with 3.5 mmHg in the placebo group ( $P < 0.0001$ ); in the nonhypertensive subgroup, the respective mean changes were a reduction of 0.8 mmHg in the telmisartan group compared with an increase of 5.4 mmHg in the placebo group ( $P < 0.0001$ ).

### Main outcomes

For the primary four-fold endpoint, we did not find any difference in the effect of treatment between hypertensive and nonhypertensive patients. No significant improvement with telmisartan over placebo in both, hypertensive and

**TABLE 1. Characteristics of hypertensive and nonhypertensive patients at baseline**

	Nonhypertensive (N = 828)	Hypertensive (N = 5098)	P-value
Age	65.4 (7.3)	67.1 (7.3)	< 0.0001
BMI (kg/m <sup>2</sup> )	26.8 (4.0)	28.4 (4.9)	< 0.0001
SBP sitting (mmHg)	123.8 (10.3)	143.8 (15.8)	< 0.0001
DBP sitting (mmHg)	74.4 (7.9)	83.1 (9.9)	< 0.0001
Pulse pressure (mmHg)	49.3 (9.6)	60.7 (13.3)	< 0.0001
Pulse rate sitting (beats/min)	66.9 (10.8)	69.1 (11.9)	< 0.0001
Urinary albumin/creatinine ratio (mg/g Crea) <sup>a</sup>	3.6 (2.0–7.5)	4.7 (2.4–12.1)	< 0.0001
Sex (female)	218 (26.3%)	2328 (45.7%)	< 0.0001
Ethnic origin			0.0003
Asian	193 (23.3%)	1068 (21.0%)	
Arab	11 (1.3%)	66 (1.3%)	
African	7 (0.8%)	99 (1.9%)	
European	529 (65.2%)	3092 (61.9%)	
Native or Aboriginal	77 (9.3%)	706 (13.8%)	
Other	11 (1.3%)	67 (1.3%)	
Tobacco use	101 (12.2%)	480 (9.4%)	< 0.0001
Smoker	440 (53.1%)	2116 (41.5%)	
Ex-smoker			
Alcohol consumption	304 (36.7%)	1549 (30.4%)	0.0003
Reasons for study entry			
Coronary artery disease	727 (87.8%)	3691 (72.4%)	< 0.0001
Peripheral arterial disease	80 (9.7%)	592 (11.6%)	0.10
Previous stroke	87 (10.5%)	887 (17.4%)	< 0.0001
TIA (> 7 days and < 1 year)	14 (1.7%)	245 (4.8%)	< 0.0001
High-risk diabetes	125 (15.1%)	1368 (26.8%)	< 0.0001
Clinical history			
Myocardial infarction	547 (66.1%)	2194 (43.1%)	< 0.0001
Stroke/TIA	110 (13.3%)	1192 (23.4%)	< 0.0001
Hypertension	0 (0%)	4528 (88.9%)	< 0.0001
Diabetes	193 (23.3%)	1925 (37.8%)	< 0.0001
Angina	413 (49.9%)	2411 (47.3%)	0.17
Medications at baseline			
ASA	675 (81.5%)	3748 (73.6%)	< 0.0001
β-Blockers	512 (61.8%)	2941 (57.7%)	0.025
α-Blockers	16 (1.9%)	220 (4.3%)	0.001
Diuretics	142 (17.1%)	1812 (35.6%)	< 0.0001
Calcium channel blockers	88 (10.6%)	1754 (34.4%)	< 0.0001
Statins	548 (66.2%)	2724 (53.5%)	< 0.0001

Data are mean (SD, *t*-tests) or *n* (%; Chi<sup>2</sup> test). TIA, transient ischemic attack.

<sup>a</sup>For patients with UACR data (N = 761, N = 4651), median and interquartile range, Wilcoxon rank sum test.

nonhypertensive patients was seen (Table 2, Fig. 1). This is similar to the result obtained in the overall population of TRANSCEND [1], although we had adjusted for confounding factors as described in the Statistical Analysis section. For the three-fold endpoint, the interaction test did not show a differential effect of telmisartan between the two subgroups. Despite the reduced sample size, in the subgroup of hypertensive patients, telmisartan reduced the occurrence of the three-fold endpoint compared with placebo (−14%, *P* = 0.05) to a similar extent as described previously in the overall patient population (−13%)

(Table 2, Fig. 1), but in the nonhypertensive group, reduction by telmisartan of the three-fold endpoint did not reach statistical significance. For MI, there was a trend for a differential treatment effect in hypertensive individuals and nonhypertensive individuals (*P* = 0.22). In hypertensive patients, but not in nonhypertensive ones, telmisartan reduced the number of MIs (HR 0.73, 95% CI 0.56–0.95, *P* = 0.021) (Table 3, Fig. 2). For the other outcomes, the effect of telmisartan was nonsignificant both across hypertensive and nonhypertensive patients, and there was no indication for any subgroup-by-treatment interaction (*P* > 0.5).

**TABLE 2. Primary and secondary outcomes**

	Telmisartan	Placebo	HR (95% CI)	<i>P</i>	<i>P</i> <sub>int</sub>
Four-fold endpoint: cardiovascular death, myocardial infarction, stroke, and hospitalization for heart failure					
Nonhypertensive subgroup	61/407 (15.0%)	68/421 (16.2%)	0.89 (0.63–1.26)	0.52	0.81
Hypertensive subgroup	404/2547 (15.9%)	436/2551 (17.1%)	0.93 (0.82–1.07)	0.33	
Three-fold endpoint: cardiovascular death, myocardial infarction, and stroke					
Nonhypertensive subgroup	52/407 (12.8%)	57/421 (13.5%)	0.91 (0.63–1.33)	0.63	0.79
Hypertensive subgroup	332/2547 (13.0%)	383/2551 (15.0%)	0.86 (0.74–1.00)	0.05	

Fully adjusted analyses. CI, confidence interval; HR, hazard ratio.

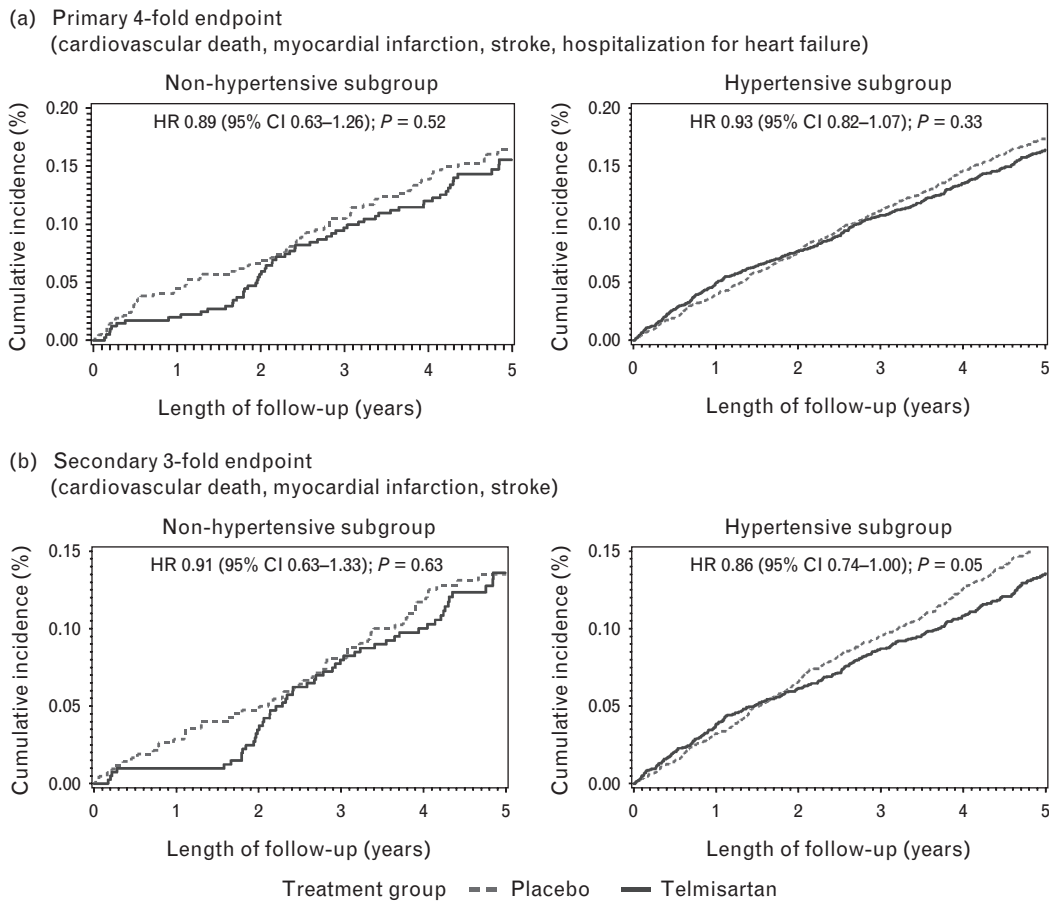


FIGURE 1 Kaplan–Meier curves for the primary (a) and secondary outcomes (b) in hypertensive and nonhypertensive patients.

**Effect of time**

Consideration of the timing of events ( $\leq 6$  vs.  $> 6$  months) in hypertensive patients revealed a difference in the treatment effect during the first 6 months compared with the later time period, as shown by the significant interactions for the primary and secondary outcomes (Fig. 3). After 6 months, there is an advantage of telmisartan for the three-fold endpoint (HR 0.80, 95% CI 0.69–0.94,  $P = 0.0072$ ) and for MI (HR 0.65, 95% CI 0.49–0.86,  $P = 0.0031$ ), and a similar trend is also observed for the four-fold endpoint (HR 0.88, 95% CI 0.76–1.02,  $P = 0.082$ ) (Fig. 3).

**Safety**

Table 4 shows the reasons for drug discontinuation during the study. Permanent discontinuations with telmisartan were less than with placebo in hypertensive patients and not different in the nonhypertensive group, highlighting the fact that telmisartan was well tolerated in both populations. Hypotensive symptoms were more frequent with telmisartan among the nonhypertensive population, whereas syncope were more frequent in hypertensive patients treated with telmisartan compared with those who received placebo. In the telmisartan group, more cases of diarrhea were reported than in the placebo group in hypertensive patients.

TABLE 3. Components of the primary outcome

	Telmisartan	Placebo	HR (95% CI)	P	$P_{int}$
Cardiovascular death					
Nonhypertensive subgroup	33/407 (8.1%)	36/421 (8.6%)	0.90 (0.56–1.46)	0.68	0.61
Hypertensive subgroup	193/2547 (7.6%)	186/2551 (7.3%)	1.03 (0.85–1.27)	0.74	
Myocardial infarction					
Nonhypertensive subgroup	18/407 (4.4%)	15/421 (3.6%)	1.16 (0.59–2.31)	0.66	0.22
Hypertensive subgroup	97/2547 (3.8%)	130/2551 (5.1%)	0.73 (0.56–0.95)	0.021	
Stroke					
Nonhypertensive subgroup	9/407 (2.2%)	11/421 (2.6%)	0.87 (0.36–2.11)	0.76	0.94
Hypertensive subgroup	102/2547 (4.0%)	125/2551 (4.9%)	0.84 (0.65–1.09)	0.20	
Hospitalization for heart failure					
Nonhypertensive subgroup	22/407 (5.4%)	21/421 (5.0%)	1.01 (0.55–1.86)	0.97	0.89
Hypertensive subgroup	112/2547 (4.4%)	107/2551 (4.2%)	1.06 (0.81–1.38)	0.68	

CI, confidence interval; HR, hazard ratio.

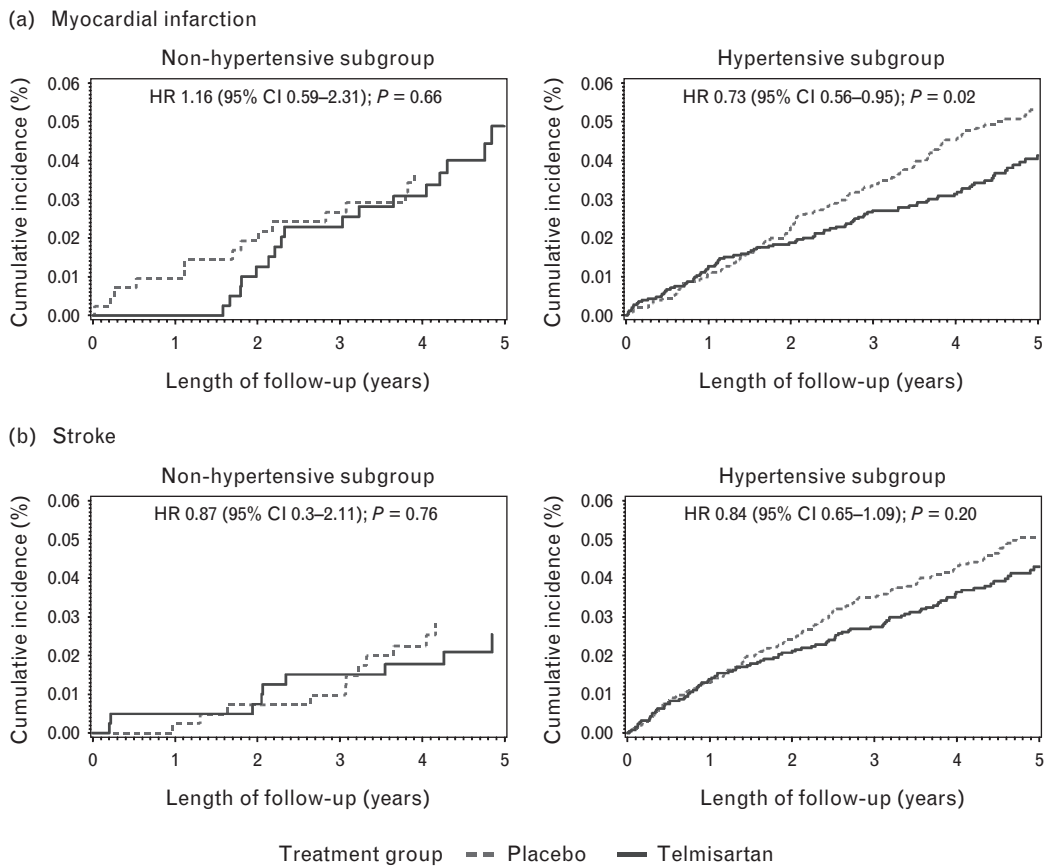


FIGURE 2 Kaplan–Meier curves for myocardial infarction (a) and stroke (b) events in hypertensive and nonhypertensive patients.

**Prevention of risk indicators**

As already reported for the total TRANSCEND patient population [5], new onset of LVH, evaluated by ECG, was significantly less in hypertensive and nonhypertensive patients treated with telmisartan (hypertensive

patients:  $-36\%$ ,  $P=0.0002$ ; nonhypertensive patients:  $-58\%$ ,  $P=0.027$ ) (Table 5).

Albuminuria increased less with telmisartan than with placebo in the hypertensive population, as the risks for new microalbuminuria and macroalbuminuria were lower than

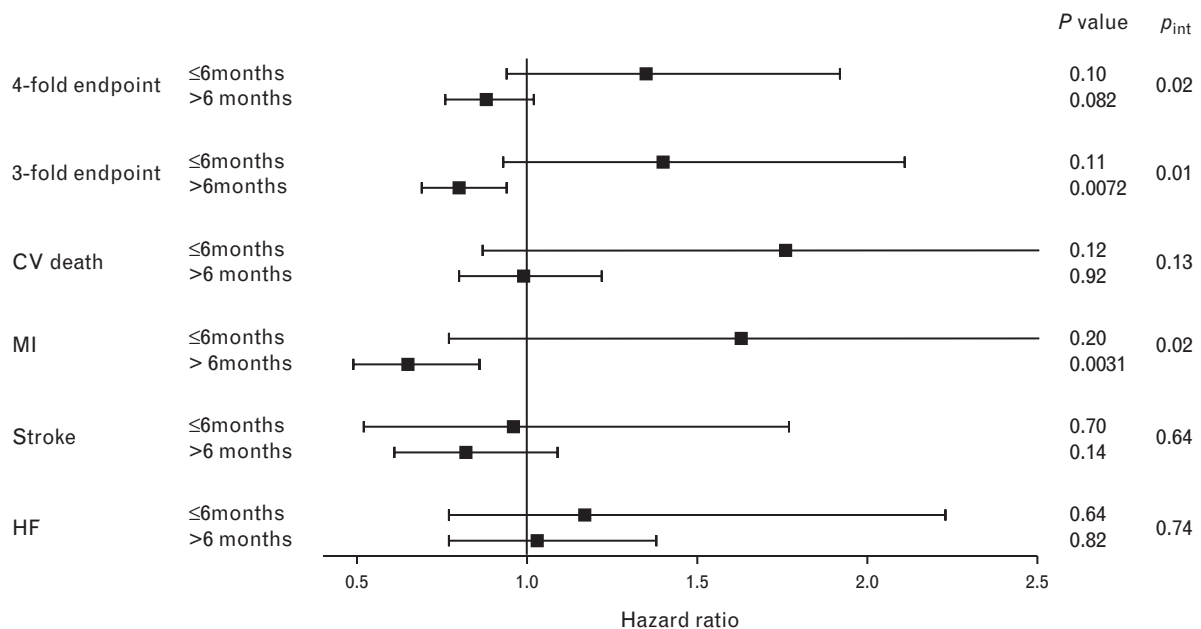


FIGURE 3 Outcomes in hypertensive patients receiving telmisartan stratified by first 6 months vs. follow-up after 6 months.  $p_{int} = p_{interaction}$ .

**TABLE 4. Reasons for drug discontinuation**

	Telmisartan	Placebo	RR (95% CI)	P	<i>P</i> <sub>int</sub>
Permanent discontinuations					
Nonhypertensive subgroup	79/407 (19.4%)	70/421 (16.6%)	1.17 (0.87–1.56)	0.30	0.074
Hypertensive subgroup	444/2547 (17.4%)	506/2551 (19.8%)	0.88 (0.78–0.99)	0.028	
Patients with SAEs on study medication					
Nonhypertensive subgroup	222/407 (54.6%)	260/421 (61.8%)	0.88 (0.79–0.99)	0.035	0.064
Hypertensive subgroup	1559/2547 (61.2%)	1570/2551 (61.5%)	0.99 (0.95–1.04)	0.81	
Patients with cough					
Nonhypertensive subgroup	1/407 (0.3%)	5/421 (1.2%)	0.21 (0.02–1.76)	0.11	0.16
Hypertensive subgroup	15/2547 (0.6%)	16/2551 (0.6%)	0.94 (0.47–1.90)	0.86	
Patients with hypotensive symptoms					
Nonhypertensive subgroup	27/407 (6.6%)	10/421 (2.4%)	2.79 (1.37–5.70)	0.003	0.042
Hypertensive subgroup	58/2547 (2.3%)	47/2551 (1.8%)	1.24 (0.84–1.81)	0.27	
Patients with syncope					
Nonhypertensive subgroup	6/407 (1.5%)	5/421 (1.2%)	1.24 (0.38–4.04)	0.72	0.87
Hypertensive subgroup	37/2547 (1.5%)	16/2551 (0.6%)	2.32 (1.29–4.15)	0.004	
Patients with diarrhea					
Nonhypertensive subgroup	2/407 (0.5%)	0/421 (0%)			0.78
Hypertensive subgroup	18/2547 (0.7%)	7/2551 (0.3%)	2.58 (1.08–6.16)	0.027	

*P*<sub>int</sub> is *P*-value of the Breslow–Day test. CI, confidence interval; RR, relative risk; SAEs, serious adverse events.

with placebo ( $P=0.0004$  and  $P=0.009$ , respectively) (Table 5). In the nonhypertensive population, the risks were not modified by the treatment. However, according to the interaction tests, there is no difference in the effect of telmisartan in hypertensive and nonhypertensive patients, suggesting that telmisartan might also reduce the new onset of microalbuminuria and macroalbuminuria in nonhypertensive patients.

## DISCUSSION

This post-hoc analysis was performed to explore if the effect of telmisartan was different in patients at high cardiovascular risk with and without hypertension. As reported earlier for the overall TRANSCEND population [1], no significant improvement of the primary outcome (cardiovascular death, MI, stroke, or hospitalization for heart failure) by telmisartan compared with placebo was seen. However, similar to the whole patient population [1], there was a borderline reduction in the secondary three-fold outcome (cardiovascular death, MI, and stroke) under telmisartan, compared with placebo treatment in the hypertensive population subgroup. However, data from this post-hoc analysis suggest that MI may be further reduced by telmisartan in hypertensive patients but not in nonhypertensive patients. These reductions observed with telmisartan for the secondary three-fold outcome and MI in the

hypertensive subgroup were even more pronounced in the follow-up period after 6 months, and a similar trend in favor of telmisartan was also observed for the primary outcome.

Current guidelines for hypertension treatment recommend to maintain BP below 140/90 mmHg (SBP/DBP) in all hypertensive patients [6]. The benefit from BP lowering below 130/80, in agreement with the previous recommendations, was controversial. In fact, except for stroke in which risk is directly correlated to SBP, the relationship between SBP and outcomes of cardiovascular death and MI seems to follow a J-curve with a nadir around 130 mmHg [7]. A post-hoc analysis of the Ongoing Telmisartan Alone and in Combination with Ramipril Global End-point Trial (ONTARGET) has demonstrated that a higher rate of BP control in this high cardiovascular-risk population led to fewer cerebrovascular and renal events, but no reduction in other cardiovascular events (MI, heart failure, or overall cardiovascular events) [8]. The authors hypothesized that this differential effect is due to a less pronounced ability of heart to maintain its perfusion at low BP values compared with the brain, which is strongly supported by the auto-regulation of cerebral blood flow [8]. The J-curve phenomenon in antihypertensive therapy is still controversial, however. Interestingly, in our post-hoc analysis, despite a 4–6 mmHg reduction in SBP achieved by telmisartan throughout the study in both subgroups, stroke events were not significantly reduced. However, in this post-hoc

**TABLE 5. New onsets of left ventricular hypertrophy, microalbuminuria, and macroalbuminuria**

	Telmisartan	Placebo	RR (95% CI)	P	<i>P</i> <sub>int</sub>
New onset of LVH (ECG)					
Nonhypertensive subgroup	8/345 (2.3%)	20/359 (5.6%)	0.42 (0.19–0.93)	0.027	0.31
Hypertensive subgroup	108/2002 (5.4%)	164/1955 (8.4%)	0.64 (0.51–0.81)	0.0002	
New microalbuminuria					
Nonhypertensive subgroup	24/386 (6.2%)	27/386 (7.0%)	0.81 (0.47–1.50)	0.46	0.76
Hypertensive subgroup	252/2249 (11.2%)	336/2268 (14.8%)	0.74 (0.63–0.88)	0.0004	
New macroalbuminuria					
Nonhypertensive subgroup	6/406 (1.5%)	8/416 (1.9%)	0.70 (0.24–2.03)	0.51	0.89
Hypertensive subgroup	60/2505 (2.4%)	93/2511 (3.7%)	0.65 (0.47–0.90)	0.009	

CI, confidence interval; LVH, left ventricular hypertrophy; RR, relative risk.

analysis, telmisartan reduced the number of MI in hypertensive patients but not the number of cardiovascular deaths or hospitalization for heart failure.

The results from this post-hoc analysis let us suggest that telmisartan may exert beneficial effects on MI in hypertensive patients. It revives thus the question as to whether or not ARBs are effective in preventing MI. The so-called ARB-MI paradox reported by Verma and Strauss in 2004 [9], which suggested that ARBs may increase the risk of MI, has not been supported by several large meta-analysis [10–12]. These studies demonstrated that ARBs are comparable to other drug classes, including ACE inhibitors, regarding their lack of an adverse effect on risk for MI. This post-hoc analysis also suggests that in hypertensive patients at high cardiovascular risk, treatment with telmisartan on top of standard therapies may reduce the risk of MI.

Moreover, we found a reduction of new onset of LVH in patients treated with telmisartan in both subgroups. This is in accordance with previous findings on the whole TRANSCEND population. In a previous subanalysis of LVH in TRANSCEND, telmisartan was superior to placebo in preventing LVH in individuals at high vascular risk, independently of any changes in BP [5]. As hypothesized by the authors, this beneficial effect could be generated by the stimulation of unopposed angiotensin AT<sub>2</sub> receptors (AT<sub>2</sub>R) by angiotensin II during AT<sub>1</sub>R blockade. Another hypothesis for the cardioprotective actions of telmisartan builds on the modulation of the peroxisome proliferator-activated receptor- $\gamma$  (PPAR- $\gamma$ ) activity featured by telmisartan [13–17]. In a rat model of MI, telmisartan has been shown to improve left ventricular remodeling independently of any BP changes via the reduction of post-MI cardiac hypertrophy and fibrosis [18]. This resulted from AT<sub>1</sub>R blockade and an anti-inflammatory effect mediated by PPAR- $\gamma$  activity [18]. Although such actions have to be confirmed in human, it is, however, already known that telmisartan is able to regulate the expression of PPAR- $\gamma$  target genes in patients with metabolic syndrome [19]. Indirect AT<sub>2</sub>R stimulation and modulation of PPAR- $\gamma$  activity may both be involved in the cardioprotective actions of telmisartan.

The present analysis also highlights a reduction of new onset of microalbuminuria/macrolalbuminuria in hypertensive patients treated with telmisartan. A similar, albeit non-significant, tendency was observed in the nonhypertensive group. In the overall population, the effect of telmisartan on renal outcomes has been already investigated [20]. In that substudy, the incidence of the main outcome (composite outcome of dialysis or doubling of serum creatinine) was similar with telmisartan and placebo. However, the risk for new microalbuminuria, macrolalbuminuria, or both was lower with telmisartan than with placebo (RR 0.77, 95% CI 0.67–0.88,  $P=0.001$ ). These and the present results are in accordance with the observation of the The Randomized Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) trial in which treatment with olmesartan medoxomil of patients with type 2 diabetes and normoalbuminuria was associated with a delayed onset of microalbuminuria (HR, 0.77; 95% CI 0.63–0.94,  $P=0.01$ ) [21]. Telmisartan may thus be effective in preventing the

development of microalbuminuria in patients at high cardiovascular risk.

This post-hoc study has several limitations. First one should know that results obtained from subanalysis of a primary study have to be carefully interpreted, and that they can only be used to generate and discuss new hypothesis. Secondly, the TRANSCEND population was at high cardiovascular risk, and it could thus be expected that a majority of the population was hypertensive. Subsequently, the number of patients in the two subgroups of the present study was unbalanced. Therefore, statistical analyses in the nonhypertensive subgroup may lack the statistical power to show differences between treatments. Moreover, the present observations were limited to approximately 5 years (median 56 months). This could hide a part of the protective actions provided by telmisartan because the superiority of telmisartan over placebo for some of the main endpoints started to be significant after 6 months of treatment. Thus, it might be possible that the BP-independent protective actions of telmisartan may need more time to translate into a decrease in cardiovascular outcomes. Finally, as described already in the results, many patients from the nonhypertensive subgroup received BP-lowering drugs at baseline. Thus, some of them, included in the so-called nonhypertensive subgroup, may in reality be hypertensive patients with controlled BP. Our criterion to define hypertensive patients was based on the medical history of hypertension and the sitting BPs at the start of the run-in.

## Perspectives

The primary and secondary outcomes in hypertensive and nonhypertensive patients were not different from the overall population of TRANSCEND. This post-hoc analysis suggests that telmisartan – on top of standard treatment may reduce the risk of MI in hypertensive patients at high cardiovascular risk. Further investigations are needed to study the hypotheses raised by this explanatory analysis.

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## Conflicts of interest

M.B., R.S., and T.U. have received consulting, lecture fees, and research grants from Boehringer Ingelheim and other companies manufacturing angiotensin receptor blockers, angiotensin-converting enzyme inhibitors, and other blood pressure-lowering drugs. K.T. has received honoraria from Boehringer Ingelheim. H.S. is an employee of Boehringer Ingelheim working as a statistician. P.S. has received grant support for the ISIS1 to ISIS4, HPS, SEARCH, HOPE, and ONTARGET/TRANSCEND trials from BHF, UK MRC, Canadian MRC, Ontario Heart and Stroke Foundation, AstraZeneca, Aventis, Boehringer Ingelheim, BMS, GSK, Monarch, MSD, National Vitamin E Association, and Roche; speaker fees or Data and Safety Monitoring Board fees from Abbott, AstraZeneca, Aventis, Bayer, Boehringer Ingelheim, Boehringer Mannheim, BMS, Genentech, GSK, Knoll,



Medscape, Menarini, Merck, Monarch, MSD, Novartis, Pfizer, Pharmacia, Sanofi, and Servier; and speaker bureau fees or stock/stock options from NIL. S.Y. has received grants, honoraria, and consulting fees from Boehringer Ingelheim, Sanofi, BMS, Servier, and GSK for studies related to CVD prevention. Dr S.F. reports no conflicts.

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## Reviewers' Summary Evaluations

### Reviewer 1

The main strengths of this paper are that it presents data from a large and rigorously conducted randomised clinical trial. Its main limitations are that the data are all posthoc subgroup analyses, with subgroups of subgroups, and are all observational. The results are therefore hypothesis generating, and not conclusive.

### Reviewer 2

The strength of this study is that it is clearly stated that the analyses are post hoc and should only be regarded as hypothesis generating. The weakness of this paper is that a large number of subgroup analyses are performed on outcomes that did not show a significant treatment effect in the main study. Also, the group defined as nonhypertensives included patients with hypertension.