Original Article

LESSONS FROM ONTARGET

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Key words: ONTARGET trial, cardiovascular, telmisartan, ramipril, RAAS

ABSTRACT

The recently published results of the ONTARGET trial shed a new light on the cardiovascular protection of patients at high risk of a cardiovascular event.

Despite a number of trials looking at the efficacy of Angiotensin Converting Enzyme inhibitors (ACEis) or Angiotensin Receptor Blockers (ARBs) in the prevention of cardiovascular events in patients with specific high risk profiles, the question of the equivalence of ACEis and ARBs remained unanswered.

The ONTARGET trial has shown that telmisartan 80 mg administered for a median duration of 4.5 years to patients at high risk of developing a major cardiovascular event, is equally effective to ramipril 10 mg. In addition, telmisartan was slightly better tolerated. The comparator ramipril has been chosen as it is currently the gold standard ACEi since the results of the HOPE study, in terms of the composite outcome of cardiovascular death, myocardial infarction and stroke.

Moreover, ONTARGET is the first trial to test the hypothesis of superiority of adding an ARB (telmisartan 80 mg) to an ACEi (ramipril 10 mg) over the ACEi ramipril monotherapy in cardiovascular protection of the same broad range of high-risk patients. Surprisingly, despite a more pronounced blood pressure lowering, the combination of the two agents did not lead to an additional decrease in the number of events, but had significantly more side-effects compared to ramipril monotherapy.

ONTARGET is a landmark study, performed according to the highest statistical and clinical standards, providing compelling evidence and clear answers to two important clinical questions.

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INTRODUCTION

Atherosclerotic cardiovascular (CV) disease remains the leading cause of morbid events and death and is predicted to induce up to 25 million deaths worldwide by 2020 (1, 2). In Belgium 30,000 to 40,000 people die every year from CV disease (3). The consequences of a CV event are serious for the patient, for his environment, and for health economics. By 2050 there will be nearly twice as many Europeans over the age of 65 as there are today (4). Since the prevalence of CV disease increases steeply with age and because of the aging population there will be a high requirement for costly CV care within the near future, which represents a difficult challenge. This is why the concept of CV protection and treatments capable of reducing morbidity and mortality are so important.

Advances in CV research during the past two decades have resulted in an improved understanding of the chain of events that lead to end-stage coronary artery disease and of the central role played by angiotensin II (AII).

THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM (RAAS)

The RAAS was already described 100 years ago. It plays a major role in volume homeostasis and blood pressure control. The central effector peptide of the RAAS, AII is formed from angiotensin I (AI) under the action of angiotensin-converting enzyme (ACE) and exerts its main actions via 2 receptor subtypes, designated angiotensin II receptor type 1 (AT_1) and type 2 (AT_2).

Stimulation of the widely expressed AT_1 receptor by AII (figure 1) produces vasoconstriction, vascular and cardiac hypertrophy, aldosterone release, sodium retention by the renal tubules and changes in renal perfusion (5-9). On the other hand RAAS is implicated in the development of CV disease through different pathophysiological processes including atherosclerosis and adverse remodelling of the damaged heart (10,11). AII-mediated stimulation of the AT_1 receptors promotes oxidative stress and endothelial dysfunction, promotes

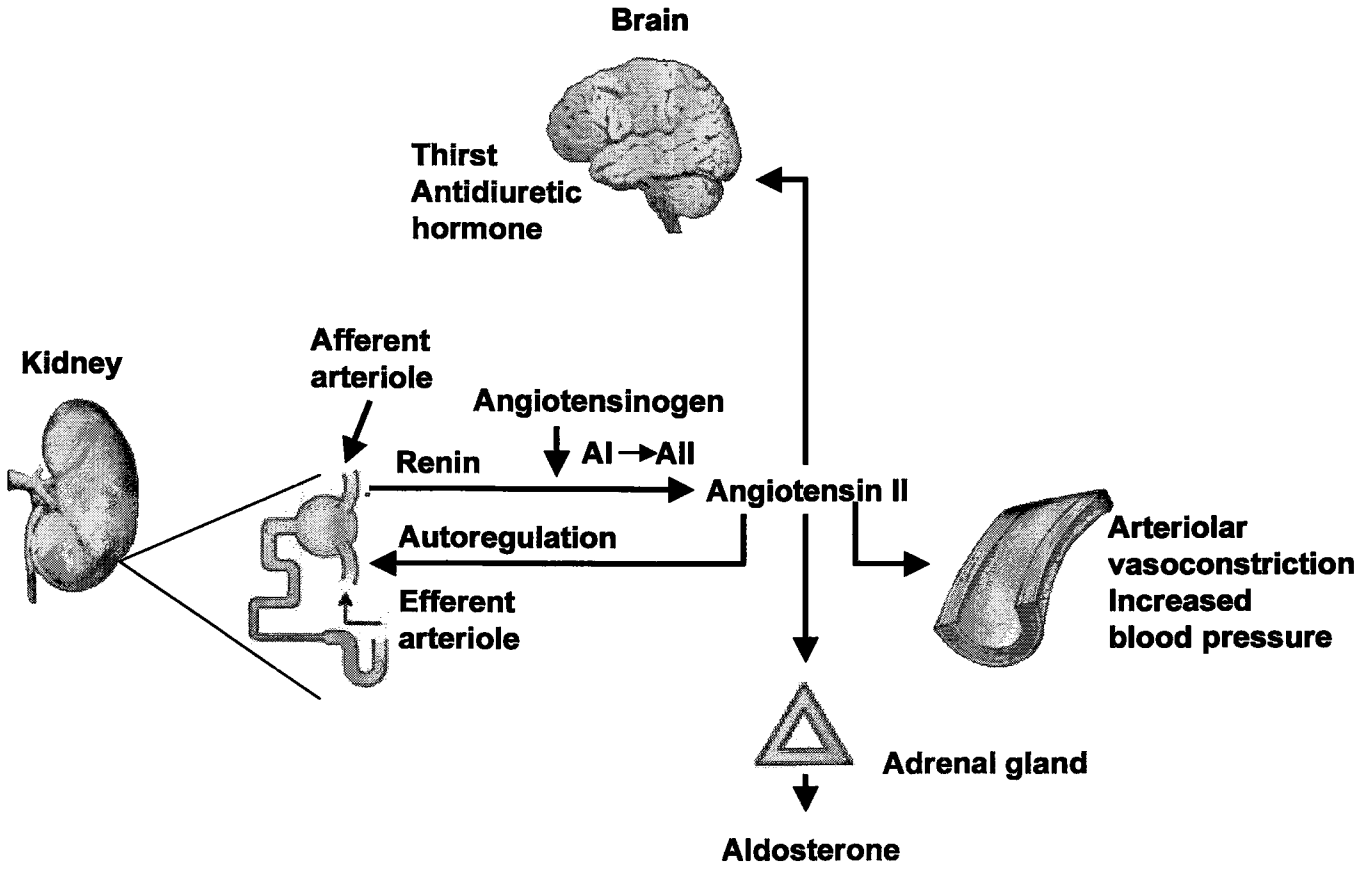

Figure 1. The Renin-Angiotensin-Aldosterone System: role of Angiotensin through the AT1 receptor.

an inflammatory response, and adversely alters the balance between the thrombotic and fibrinolytic state (12). The process of CV disease, from the onset to end-stage heart disease, shows a progression and can be regarded as a continuum (figure 2).

Conversely, AT_2 receptors, which have a more limited distribution and expression in normal adult tissues, appear to be involved in the control of cell proliferation, differentiation and development, angiogenesis, tissue regeneration, and even apoptosis (9,13-17). Expression of AT_2 has been seen to be upregulated in CV pathological processes such as heart failure and postinfarct repair (18).

INHIBITION OF THE RAAS

Because of the involvement of the RAAS – and more precisely AII – in most steps of the CV continuum, agents able to modulate this system have been developed. Both angiotensin-converting enzyme inhibitors (ACEis) and angiotensin AT_1 receptor blockers (ARBs) have proved their efficacy in lowering blood pressure (BP) and suppressing most of the AII deleterious effects (7,19). ACEis act by blocking the ACE-mediated conversion of AI to AII; they also prevent the breakdown of bradykinin, a vasodilatory peptide (7, 20). Bradykinin has been shown to have beneficial effects associated with the release of nitric oxide (NO) and prostacyclin, which produces vasodilation and may contribute to the BP-lowering effect. It may also be responsible, however, for some of the ACEi-related adverse effects, such as dry cough, hypotension and angioedema (21). Blocking AII formation through ACE inhibition is hampered by a new rise in plasma AII levels after initial suppression (22), through mechanisms independent of the converting enzyme. These non-ACE-mediated pathways (e.g. chymase, cathepsin-sensitive angiotensin generating enzyme), continue to produce AII, a phenomenon referred to as 'AII escape' (23).

ARBs completely and selectively antagonize the AT_1 receptors so that whatever the origin of AII, its action is blocked. ARBs induce a dose-dependent blockade of AII-induced effects at the AT_1 receptor (24, 25). This type of blockade therefore offers a potentially more complete interruption of the AT_1-mediated negative effects of AII than what can be reached with ACEi. The AT_2 receptors, when stimulated by AII, are thought to have opposing effects to the AT_1 receptors and hence have mainly beneficial effects in the CV system (25) and tissue-protective effects beyond the effects on BP. Indeed they are known to inhibit cell proliferation and to reverse AT_1-

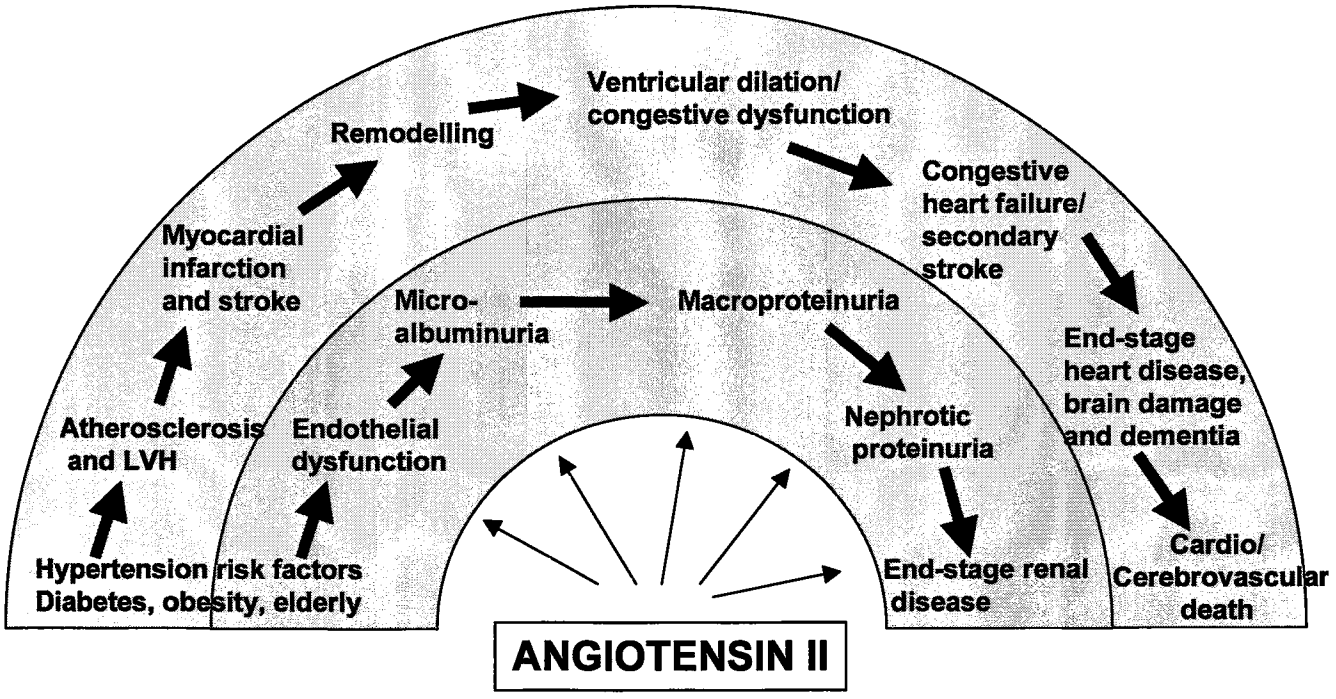

Figure 2. Cardiovascular disease:Role of angiotensin II in the CardioVascular continuum. Adapted from Dzau V, Braunwald E, Am Heart J 1991;121:1244–63

induced hypertrophy and thought to modulate neuroplasticity, vascular regeneration and to promote apoptosis (9,15,18,25). Recent studies, however, have suggested that the biology of AT_2 receptors is more complex than previously believed so that the effects of AII via the AT_2 receptors are currently being debated (26).

RATIONALE FOR DUAL BLOCKADE OF THE RAAS

The rationale for combining ACE inhibition and Angiotensin Receptor Blockade (i.e. the concept of "dual RAAS blockade") is to benefit from each type of treatment and to increase clinical efficacy by the complementary action of the two different pathways involved. ACE inhibition decreases circulating and tissue AII and potentiates the effects of bradykinin, including generation of NO. The protective effects of ARBs, on the other hand, result from complete blockade of the AT_1 receptors and potentially also from stimulation of the AT_2 receptors.

With combined ACE inhibition and AT_1 receptor antagonism, bradykinin levels will increase due to ACE inhibition and, at the same time, the AT_1 receptors are selectively blocked, preventing any AII produced via alternative pathways from exerting a negative action. The low circulating level of AII could then only exert its effects through the unopposed AT_2 receptors insofar as they are expressed.

EVIDENCES OF CV PROTECTION BY RAAS INHIBITION

ACEis were first developed to lower BP, but soon proved to have broader beneficial CV effects such as reduction of heart failure (27,28). Large-scale studies with ACEis showed a reduction in CV risk which might not be totally explained by BP reduction alone (29-31). However, according to other authors (32,33) , the reduction of CV morbidity and mortality is largely the result of the BP reduction.

The proof of concept of CV protection with ACE inhibition was a milestone for evidence-based medicine (EBM). The Heart Outcomes Prevention Evaluation (HOPE study) (31) was the first large-scale outcome trial to show benefits using the ACEi ramipril, in preventing major CV events in high-risk patients without high blood pressure. Ramipril 10 mg daily significantly reduced the rate of CV mortality by 26%, myocardial infarction (MI) by 20% and stroke by 32%.

Since the HOPE study, ACEis and ARBs have demonstrated benefits in hypertension, congestive heart failure (CHF), acute MI with left ventricular (LV) dysfunction or diabetic nephropathy (29, 34-39). The results of these outcome studies have been conclusive enough to warrant ACEis and to a lesser extent ARBs to be recommended as first line therapeutic options for the management of patients at high risk for recurrent vascular events (40-45).

However, a benefit in vascular disease patients with preserved LV systolic function has only been demonstrated for ACEis. So, the clinically important questions which remain unanswered for the treatment of patients at high CV risk receiving optimal medical care are:

(1) Are ARBs as good as ACEis for the treatment of this group of high CV-risk patients with normal LV systolic function?

(2) Is the combination therapy of an ACEi and an ARB more beneficial compared to an ACEi given in monotherapy?

THE ONTARGET TRIAL PROGRAMME

The ONTARGET trial programme (**ON**going Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) was designed to test the hypothesis that (1) the ARB telmisartan provides similar CV protection compared to the ACE-inhibitor ramipril at the dose used in the HOPE trial, in high CV-risk patients, and (2) the combination of telmisartan plus ramipril confers additional benefits compared to ramipril alone.

The ONTARGET Trial Programme consists of two randomized, double-blind, international multi-centre outcome trials: the principal trial, ONTARGET, and a parallel trial, TRANSCEND (**T**elmisartan **R**andomized **A**ssessme**N**t **S**tudy in a**CE** i**N**tolerant subjects with cardiovascular **D**isease) trial.

The ONTARGET Trial Programme design (figure 3) and baseline characteristics have previously been published (46,47) (table 1). The inclusion criteria for the ONTARGET trial were very similar to those of the HOPE trial, i.e. patients were at least 55 years old and are at high risk of developing a major CV event because of a history of coronary artery disease, peripheral arterial occlusive disease, cerebrovascular event or diabetes mellitus with end-organ damage.

The major exclusion criteria included CHF, significant renal disease, hepatic dysfunction and uncontrolled hypertension on treatment (e.g. BP > 160/100 mmHg).

Table 1: ONTARGET baseline characteristics and comparison with HOPE

	ONTARGET (n=25,620)	HOPE (n=9541)
Demography		
Age (years)	66.4	65.9
Male (%)	73.3	73.3
Physical Exam		
BP at run-in (mm Hg)	143/82	139/79
BP at randomisation (mm Hg)	134/77	NA
Body mass index	28.2	27.7
Waist–hip ratio	0.9	0.9
Medical History		
Hypertension	68.3	46.5
MI	48.7	52.8
Stable angina	34.8	55.8
Stroke/TIA	20.7	10.8
Intermittent claudication	11.8	15.9
Diabetes	37.3	38.3
Current smoker	12.5	14.1
Medications (% of patients)		
ACE Inhibitors	57.5	11.6
Angiotensin Receptor Blockers	8.6	-
Beta-blockers	56.9	39.5
Diuretics	27.9	15.1
Nitrates	29.2	31.1
Calcium channel blockers		
- Diltiazem/verapamil	9.7	27.1
- Other	23.8	20.5
Antiplatelets		
- ASA	75.6	73.6
- Ticlodipine	2.5	4.8
- Clopidogrel	8.5	-
Oral anticoagulants	7.6	3.8
Statins	60.7	28.9
Insulin	10.4	11.7
Oral hypoglycaemics	25.0	21.8

Adapted from Teo K et al. (47).

The primary objectives of ONTARGET were to determine whether: (1) telmisartan 80 mg alone daily is non-inferior to ramipril 10 mg and (2) the combination of telmisartan 80 mg plus ramipril 10 mg is more effective than ramipril 10 mg, in reducing the primary endpoint which is the composite outcome of CV death, MI, stroke or hospitalization for CHF. Secondary and tertiary endpoints have been described elsewhere (47).

After screening and a run-in period (figure 3), patients were included either in the ONTARGET or the TRANSCEND trial. The 25,620 patients enrolled in ONTARGET were titrated to telmisartan 80 mg/day, or ramipril 10 mg/day, or a combination of telmisartan 80 mg/day and ramipril 10 mg/day on top of their baseline medications.

In the parallel trial TRANSCEND which included 5,926 patients intolerant to ACEi, telmisartan 80 mg/day was tested against placebo. Its primary objective is to determine whether treatment with telmisartan 80 mg is superior to placebo.

Both trials have an average observation period of 4.5 years.

The results of the ONTARGET trial have been published recently (48) and are summarized below. The results of TRANSCEND are expected for September 2008.

ONTARGET RESULTS

Telmisartan versus ramipril

At a median follow-up of 56 months, the composite primary outcome of death from CV causes, MI , stroke, or hospitalization for CHF had occurred in 1412 patients (16.5%) treated with ramipril, and 1423 patients (16.7%) treated with telmisartan (table 2). The relative risk (RR) of the primary outcome in the telmisartan group as compared with the ramipril group is 1.01 (95% CI, 0.94 to 1.09). The 1.09 upper boundary is largely and significantly lower than the predefined non-inferiority boundary of 1.13 (47,48) confirming the statistical non-inferiority of telmisartan, as compared to ramipril (p=0.004).

For the main secondary outcome (composite endpoint of death from CV causes, MI and stroke) similar to the primary endpoint of the HOPE trial, telmisartan reached a RR of 0.99 (95% CI, 0.91 to 1.07) (p=0.001) (table 2).

ONTARGET showed that telmisartan preserves about 95% and 105% of the benefits of ramipril over placebo for the primary and main secondary outcomes, respectively. No significant difference was seen for each individual component of the primary outcomes (including death from any cause, death from CV and from non-CV cause). Similarly no significant difference was seen for the other predefined secondary and other outcomes such as revascularization, hospitalization for angina, worsening or new angina, new diagnosis of diabetes, heart failure, new atrial fibrillation, renal impairment, and renal failure requiring dialysis (48).

Table 2: Incidence of the Primary and Main Secondary Outcomes from ONTARGET

	Ramipril (N=8576)	Telmisartan (N=8542)	Telmisartan vs. Ramipril	
	N (%)	N (%)	RR (95% CI)	p (non-inf)
Primary Outcome				
CV Death, MI, Stroke, CHF Hosp.	1412 (16.5%)	1423 (16.7%)	1.01 (0.94-1.09)	0.0033
Main Secondary Outcome (HOPE outcome)				
CV Death, MI, Stroke	1210 (14.1%)	1190 (13.9%)	0.99 (0.91-1.07)	0.0008

Adapted from Yusuf S et al. (48).

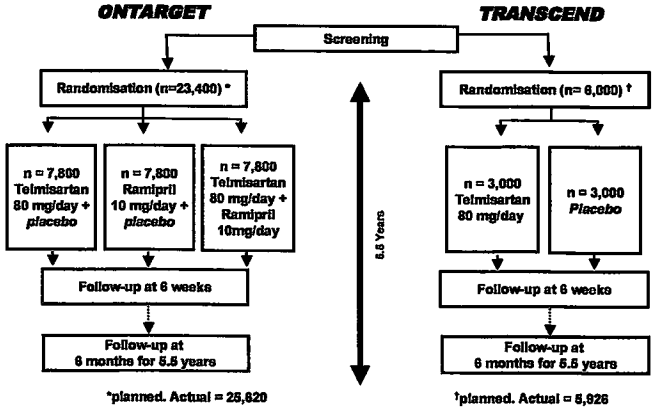

Figure 3. *The ONTARGET Trial Programme: Study design. The Ontarget/ Transcend Investigators (47)*

Key subgroups analyses (sex, age or presence of CV disease, arterial hypertension, diabetes) showed similar results for the ramipril-treated patients and the telmisartan-treated patients. These results were consistent after adjustment for the patient's use of various concomitant drugs. The results of an ongoing subgroup analysis comparing the effects of both treatments for patients with or without albuminuria will be published later.

CV protection using telmisartan was shown to be non-inferior and might be considered equivalent, in view of the results, to that offered by ramipril, and telmisartan was better tolerated. Telmisartan was associated with a lower rate of cough than ramipril (1.1% vs 4.2%, p<0.001) and of the potentially life-threatening angioedema (0.1% vs 0.3%, p=0.01). On the other hand, telmisartan showed a higher rate of hypotensive symptoms (2.7% vs.1.7%, p<0.001) but no more syncopal episodes than ramipril (0.2% in both groups). The rate of permanent discontinuations was significantly higher in the ramipril group than in the telmisartan group (table 3).

In conclusion for the comparison of the two monotherapies, telmisartan 80 mg can be considered equivalent to ramipril 10 mg in protecting against CV death, MI, stroke and CHF hospitalization. Telmisartan was safe, better tolerated than ramipril and associated with a higher persistence on therapy in a large population of patients with vascular disease or high-risk diabetes.

Combination therapy versus ramipril

The total event rate in the combination therapy group (1386 events, 16.3% of patients) was very similar to that in the ramipril group (1412 events, 16.5% of patients) with a calculated RR of 0.99 (95% CI, 0.92 to 1.07). The combination of telmisartan and ramipril did not reach superiority compared with ramipril alone despite a significantly more important BP lowering (Δ2.4/1.4 mmHg) than with the respective monotherapies. Moreover, more adverse events occurred with the combination therapy (mainly hypotensive symptoms including syncope, diarrhoea and renal impairment) leading to a significantly higher rate of permanent discontinuations of at least one of the components of the combination therapy (29.4% vs 23.7%) (table 3). Among the individual components of the primary out-

Table 3: Discontinuation of study medications

Variable	Ramipril (N=8576)	Telmisartan (N=8542)	Combination Therapy (N=8502)	Telmisartan vs. Ramipril		Combination Therapy vs. Ramipril	
	number (percent)			RR	p-value	RR	p-value
Total no. of discontinuation*	2099 (24.5)	1962 (23.0)	2495 (29.3)	0.94	0.02	1.20	<0.001
Permanent discontinuation	2029 (23.7)	1796 (21.0)	1929+566$ (22.7+6.7)				

* A patient could have multiple discontinuations, since patients were encouraged to restart study medications whenever possible after discontinuation.
$ In the combination-therapy group, there were 1929 patients discontinuing both drugs, and an additional 566 stopping 1 drug.
Adapted from Yusuf S et al. (48).

come and the secondary and other outcomes, only renal impairment was significantly different between the 2 treatment arms, showing a higher rate with the combination therapy (13.5% vs 10.2%, p< 0.001). The rate of renal dialysis (0.8% vs 0.6%, p=0.1) did nevertheless not reach significance maybe due to the low number of events. The number of deaths was also higher in the combination-therapy group than in the ramipril group (RR 1.07), but the difference was not significant. No particular cause of death reached a significant difference between the groups (48).

Likewise, comparison of pre-specified subgroups showed no difference between the combination therapy group and the ramipril group.

In conclusion, the combination therapy did not reduce the risk of CV death, MI, stroke, and hospitalization for CHF to a greater extent compared to ramipril alone. Moreover, the combination therapy was associated with a higher rate of adverse events and a trend towards a higher mortality.

DISCUSSION

ONTARGET is 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 (median 56 months). It has recruited 25,620 patients in 773 centres from 40 countries throughout Europe, North America, Africa, Australasia and Asia. ONTARGET achieved the highest number of patient years ever in an ARB or ACEi trial (approximatively 120,000), thus adding statistical weight to all the conclusions and providing compelling and indisputable evidence for any observed CV-protective effect.

The patient population with high CV risk is also the broadest ever studied in an ARB trial in terms of pathologies recruited. The trial allowed inclusion of diverse patient types for which dual RAAS blockade had never been tested on such a large scale. It is representative of a large number of patients seen in an average daily cardiology and general practice in Belgium. The primary endpoint, which is a composite of death, non-fatal MI or stroke and hospitalization for CHF is well chosen in view of the statistical power and the number of events in this events-driven trial. It also takes into account the diversity of inclusion criteria. The risk of MI after an initial stroke, for instance, is indeed at least as big as the risk of suffering a recurrent stroke (49). What matters most is to prevent any kind of event likely to interfere not only with survival but also with quality of life.

ONTARGET lived up to its expectations because it unequivocally answered the two important questions it was designed for. It is the first trial to show that the ARB telmisartan is an equally effective alternative (RR 1.01 ; 95% CI 0.94-1.09) to the reference ACEi ramipril in this study population (48). Telmisartan is the only ARB that has been evaluated in a head-to-head comparison with the gold standard ramipril in this setting. The dose of telmisartan was 80 mg per day, i.e. the maximum dose registered for the treatment of essential hypertension; the dose of ramipril was 10 mg per

day, previously proved to be effective for the prevention of vascular events in high-risk patients with CV disease or diabetes but without heart failure (31). According to the principles of evidence-based medicine (EBM) the outcome of ONTARGET cannot readily be extrapolated to other ARBs or ACEis or to doses of telmisartan and ramipril other than those used in the study. Some typical drug pharmacokinetic characteristics of telmisartan might have contributed to the clinical outcome: it has the longest half-life of all ARBs , the highest distribution volume and a very high affinity for the AT_1 receptors (50). Therefore when an ARB is considered to be the preferred treatment option for CV prevention in high CV risk patients like those studied in ONTARGET, telmisartan should be preferred to other AT_1-receptor blockers and 80 mg per day the dose to be aimed at. It is likely that future evidence-based treatment guidelines will take these arguments into account.

ONTARGET is also the first trial to show that patients with high CV risk but without symptomatic CHF do not benefit from dual RAAS blockade with ramipril and telmisartan as compared to each of the two monotherapies, despite a greater reduction in BP. Combination therapy in these patients was associated with more adverse events such as hypotension, diarrhoea and renal failure. Therefore combination therapy cannot be recommended in this type of patient.

Adverse events are a very important factor in daily practice when considering life-long treatment in patients with high-risk CV disease. ACEis have been consistently shown to be associated with a greater risk of cough than ARBs. In a recent analysis (51) the rates of cough in randomized, controlled trials were 9.9% for the ACEi group and 3.2% for the ARB group. In ONTARGET there was a significantly higher discontinuation rate because of cough in the ramipril group compared to the telmisartan group (4.2% vs 1.1%). The discontinuation rate due to cough in the ramipril group, however, was relatively low probably because of the exclusion of previously ACE-intolerant patients during the run-in phase, which probably diluted the real difference in incidence of cough between the two patient groups. Angioedema is a relatively rare but potentially life-threatening clinical condition. It led to treatment discontinuation in 0.3% (ramipril) and 0.1% (telmisartan) of patients, a statistically significant difference. Discontinuations due to hypotensive symptoms were less frequent in the ramipril (1.7%) than in the telmisartan group (2.7%) possibly due to slightly greater reductions in BP in the telmisartan group (0.9/0.6 mmHg lower than in the ramipril group over the study period). However, there was no increased incidence of syncope in the telmisartan group.

In ONTARGET, patients were encouraged to restart study medication after discontinuation. As a consequence, some discontinuations were not permanent; patients restarting telmisartan were substantially more numerous than those restarting ramipril (table 3). ONTARGET shows that telmisartan has a different and slighly better tolerability profile as compared to ramipril. It offers a safe and effective treatment alternative and a high degree of treatment adherence.

For obvious ethical reasons ONTARGET was not a placebo-controlled study. Therefore comparisons between the outcome of ONTARGET and HOPE – where ramipril was directly compared to placebo – are only possible through indirect statistical comparison. Based on the benefits of ramipril over placebo in HOPE and assuming that the patient population in ONTARGET is similar to that in HOPE, it can be extrapolated from ONTARGET that telmisartan might offer a relative risk reduction over placebo of 21% for the primary outcome (48).

The awaited outcome of TRANSCEND will shed more light on the results of ONTARGET. It will indeed show to what extent telmisartan, administered on top of today's optimal treatment (which has changed considerably since the results of HOPE were published in 2000 e.g. with the increasing use of statins), can alter the clinical outcome of high CV risk patients.

In conclusion, ONTARGET is a landmark study, performed according to the highest statistical and clinical standards, providing compelling evidence and clear answers to two important clinical questions. Firstly it shows that the ARB telmisartan 80 mg per day is as effective as the ACEi ramipril 10 mg per day in terms of preventing new CV events in high CV risk patients without heart failure and that it is slightly better tolerated. According to EBM the outcome of ONTARGET cannot be readily extrapolated to other ARBs or ACEis or to doses of telmisartan and ramipril other than those used in this study.

Secondly, it clearly demonstrates that in this same study population, the combination of telmisartan 80 mg and ramipril 10mg offers no additional benefit and is associated with more adverse effects.

Note: Telmisartan is in Belgium only approved for the treatment of hypertension.

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