

Rationale, design, and baseline characteristics of 2 large, simple, randomized trials evaluating telmisartan, ramipril, and their combination in high-risk patients: The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial/Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (ONTARGET/TRANSCEND) trials

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Background Angiotensin-converting enzyme (ACE) inhibitors reduce mortality, myocardial infarction, stroke, heart failure, need for revascularization, nephropathy, and diabetes and its complications. Although angiotensin-II receptor blockers (ARBs) have been less extensively evaluated, theoretically they may have "protective" effects similar to those of ACE inhibitors, but with better tolerability. Currently, there is uncertainty about the role of ARBs when used alone or in combination with an ACE inhibitor in high-risk populations with controlled hypertension.

Objectives Primary objectives of the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) are to determine if the combination of the ARB telmisartan and the ACE inhibitor ramipril is more effective than ramipril alone, and if telmisartan is at least as effective as ramipril. The Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (TRANSCEND) will determine if telmisartan is superior to placebo in patients who are intolerant of ACE inhibitors. The primary outcome for both trials is the composite of cardiovascular death, myocardial infarction, stroke, or hospitalization for heart failure.

Method High-risk patients with coronary, peripheral, or cerebrovascular disease or diabetes with end-organ damage are being recruited and followed for 3.5 to 5.5 years in 2 parallel, randomized, double-blind clinical trials.

Progress Recruitment from 730 centers in 40 countries for ONTARGET (n = 25,620) was completed in July 2003. For TRANSCEND, 5776 patients (out of a projected total of 6000) have been recruited (by May 10, 2004). Baseline patient characteristics are comparable to the Heart Outcomes Prevention Evaluation (HOPE) trial, the basis of the design of the current study, confirming that patients are at high-risk. (*Am Heart J* 2004;148:52-61.)

Cardiovascular disease (CVD) is a major and growing global public and social healthcare problem, accounting for 40% to 50% of all deaths in industrialized countries and about 25% in other countries.¹ Preventive

measures to reduce traditional risk factors, including hypertension, diabetes mellitus (DM), smoking, and blood cholesterol, can help substantially.^{2,3} Angiotensin-converting enzyme (ACE) inhibitors lower angiotensin II (A-II), elevate levels of bradykinin, and reduce CVD risk in high-risk individuals, resulting in increased survival and prevention of myocardial infarction (MI), strokes, revascularization procedures, heart failure, and nephropathy.⁴⁻⁶ Recent data suggest ACE inhibitors may also prevent DM, dementia, and atrial fibrillation.⁶⁻⁸

A-II receptor blockers (ARBs) are well-tolerated and effective blood pressure (BP)-lowering agents,⁹⁻¹¹ and may have many of the benefits of ACE inhibitors, with

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perhaps fewer side effects.^{11,12} The combination of an ARB with an ACE inhibitor may lead to additive effects.¹³⁻¹⁶ While producing BP reduction similar to other agents, ARBs reduce strokes in high-risk individuals with severe hypertension and left ventricular hypertrophy and increase renal protection in patients with diabetic nephropathy.¹⁷⁻²⁰ They also reduce cardiovascular (CV) death and hospitalization for congestive heart failure in patients with previous heart failure.^{14,21,22}

Herein, we describe the rationale, design, and patient baseline characteristics in 2 randomized trials to address the above concepts: the ONgoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) and the Telmisartan Randomized Assessment Study in ACE Intolerant subjects with cardiovascular Disease (TRANSCEND).

Rationale for telmisartan and ramipril

A-II, a powerful vasoconstrictor, increases BP, promotes vascular and cardiac hypertrophy, and increases risk of CVD events by means of its effects on endothelial function and atherosclerosis.^{4,9-11} Additionally, A-II increases the inflammatory processes in vessels and precipitates acute coronary syndromes.^{23,24} ACE inhibitors reduce A-II but increase levels of bradykinin, although the clinical importance of the latter is unclear.

Blockade of angiotensin-receptor subtype 1 (AT₁) by ARBs may also reduce the deleterious effects of A-II, but with a reflex increase in A-II levels and activation of other A-II receptors subtypes; the latter may lead to important antigrowth and antitissue proliferation actions.^{4,9,25} ACE inhibitors do not completely block the renin-angiotensin system (RAS), because A-II is produced via other non-ACE-mediated pathways. ARBs also suppress various inflammatory and atherogenesis markers, such as vascular cell adhesion molecules, tumor necrosis factor- α , and superoxide.²⁴ A combination of the 2 agents may be more effective clinically than either one alone; recent trials show promising results.^{13-16,21,22}

The recent European Trial on the Reduction of Cardiac Events with Perindopril in Patients with Stable Coronary Artery Disease (EUROPA)²⁶ included patients with baseline characteristics comparable to those in the Heart Outcomes Prevention Evaluation (HOPE) trial.⁶ Treatment with perindopril was associated with a reduction in the composite primary outcome of CV death, MI, or cardiac arrest;²⁶ as in HOPE, these effects did not appear to be explained by BP reduction alone.²⁷ The Second Australian Blood Pressure Lowering Trial (ANBP2)²⁸ showed that, in hypertensive patients, treatment with an ACE inhibitor was associated with a significant reduction in CVD events compared to a diuretic-based regimen for the same BP reduction.

ACE inhibitors can potentially reduce the risk of atrial fibrillation, cognitive decline, and dementia.^{7,8}

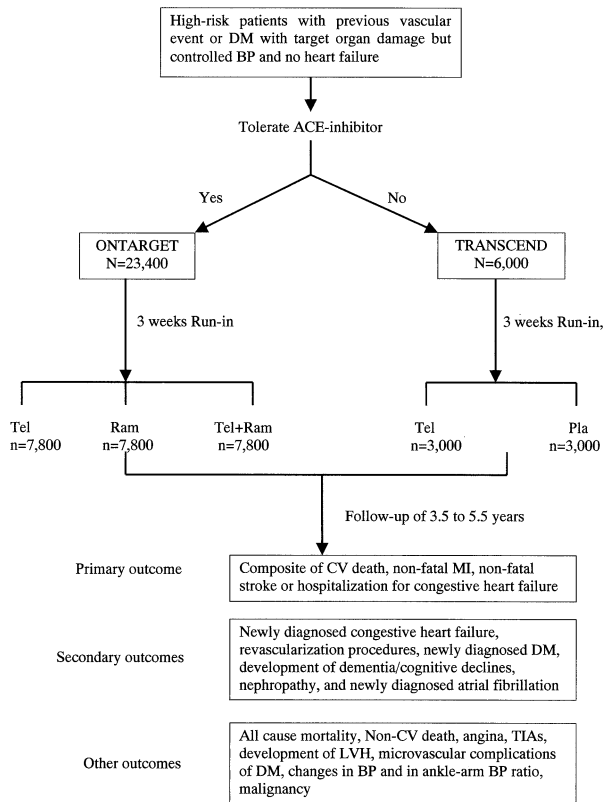
ARBs may have similar protective clinical effects as ACE inhibitors, but may be better tolerated.^{12,29} Several studies indicate lower rates of cough with ARBs compared to ACE inhibitors; however, recent studies suggest that the rates of elevated creatinine and potassium levels, or angioedema, may be considerable.^{13,14,21,22,30} Despite these concerns, in 3 trials on hypertensive patients with DM and various degrees of renal impairment, ARBs (irbesartan or losartan) significantly reduced serum creatinine and/or development of end-stage renal failure, compared to placebo or amlodipine, again with similar levels of BP control.^{17,19,20} The Losartan Intervention For Endpoint reduction (LIFE) trial¹⁸ compared losartan with atenolol in individuals with severe hypertension and electrocardiographic evidence of left ventricular hypertrophy; losartan significantly reduced the primary composite end point of CV mortality, stroke, or MI, although both agents produced substantial and comparable BP reductions. Losartan significantly reduced the incidence of new-onset DM.¹⁸

The Candesartan in Heart Failure Assessment in Reduction of Mortality (CHARM) program^{13,14,21,22} consists of 3 separate trials evaluating the effects of a combination of ACE inhibitor and an ARB, candesartan (CHARM-Added), candesartan alone in ACE-intolerant patients (CHARM-Alternative) and candesartan in patients with preserved LV function (CHARM-Preserved). These further confirm the benefits of candesartan in heart failure patients, and show clearly that candesartan (1) is highly efficacious when used alone on a background of other proven therapy in heart failure patients with LV systolic dysfunction, and (2) additional benefits can be obtained when added to an ACE inhibitor in these patients, but (3) in CHARM-Preserved, the effect of added candesartan on the primary outcome of CV death and heart failure hospitalization is less clear.

The Valsartan in Acute Myocardial Infarction Trial (VALIANT),³⁰ which enrolled patients with heart failure or left ventricular dysfunction during the immediate postinfarction period, compared the effects of captopril and valsartan. Valsartan alone was similar to captopril alone. The combination of captopril and valsartan was not superior to captopril alone but had more drug-related adverse effects, particularly hypotension, renal dysfunction, and hyperkalemia. In the unstable situation after MI, the combination may have lowered BP too aggressively.

The inconsistency between the results of CHARM and VALIANT and uncertainty concerning the protective effects of ARBs when used alone or in combination with an ACE inhibitor in less high-risk populations with controlled hypertension form the basis for the

Figure 1



Study design and outcomes. DM, Diabetes mellitus; BP, blood pressure; Tel, telmisartan; Ram, ramipril; Pla, placebo; CV, cardiovascular; MI, myocardial infarction; TIAs, transient ischemic attacks; LVH, left ventricular hypertrophy.

present study, which will also explore the impact of ARBs on DM, atrial fibrillation, and dementia. The ONTARGET and TRANSCEND trials address these issues in high-risk individuals with baseline BP considered to be in the “normal” range.

Study design

Objectives

The ONTARGET and TRANSCEND trials compare an ACE inhibitor versus ARB versus a combination of both in high-risk individuals. The patients enrolled already receive a number of proven therapies. The primary objectives of ONTARGET are to determine if (1) the combination of telmisartan 80 mg daily and ramipril 10 mg daily is more effective in reducing the composite outcome of CV death, MI, stroke, or hospitalization for CHF than ramipril 10 mg alone; and (2) whether telmisartan 80 mg daily alone is at least as effective as (ie,

Table I. Summary of substudies

Title of substudy	Objectives
Biological samples collection for central laboratory analysis	Collection and storage of blood samples at baseline for analysis of novel risk factors and markers for cardiovascular disease.
Oral glucose tolerance test (OGTT)	OGTT carried out in all TRANSCEND patients who are not known to have DM at baseline, 2 years follow-up and close-out. In a subsample, insulin sensitivity will be determined.
Health economics	To determine resources used and direct medical costs associated with clinical events; to evaluate the impact of treatment program on patient preference.
Ambulatory blood pressure monitoring	To determine prognostic value of ambulatory blood pressure monitoring; to determine the effects of study medications.
Cardiac MRI	To examine effects of treatment on cardiac structure and function.
Arterial Stiffness	To determine efficacy of telmisartan on arterial stiffness, estimated by pulse wave velocity.
Erectile dysfunction	To examine the effects of treatment on erectile dysfunction.

“not inferior” to) ramipril 10 mg alone daily. The primary objective of TRANSCEND is to determine if treatment with telmisartan 80 mg daily is superior to placebo in patients who are intolerant of ACE inhibitors. A number of secondary and other objectives (Figure 1) and 7 embedded substudies (Table I) are included.

Sample size and data analysis issues

Sample size calculations are based on the event rates in the ramipril group of HOPE, in which the hazard rate was 0.0397 per year. The 2 objectives of ONTARGET are being addressed by showing that the hazard ratio of the combination versus ramipril is <1 (superiority) and that the hazard ratio of telmisartan versus ramipril is less than a predefined margin Δ , a value ensuring that most of ramipril’s effect versus placebo is retained by telmisartan (noninferiority).

Determination of Δ was based on the results of the HOPE trial.⁶ In HOPE, the hazard ratio for ramipril 10 mg versus placebo with respect to the same composite end point was 0.775. Risk reductions of the same magnitude have been observed in other studies comparing ACE inhibitors with placebo,^{5,31} thus assuring consistency with the HOPE results. Taking a conservative approach, the 40th percentile (0.794) rather than the observed hazard ratio is chosen as a more robust reference to describe the ramipril effect. The risk reduction by ramipril versus placebo is translated into an excess risk of placebo versus ramipril of 1.26. Thus, a Δ of 1.13 assures that telmisartan retains at least half of the ramipril effect if the upper limit of the 95% CI of the

hazard ratio of telmisartan vs ramipril is less than this Δ .³² Once noninferiority has been confirmed, it is then possible to evaluate if telmisartan is superior to ramipril.

Both hypotheses will be tested using group sequential tests at a 1-sided level of $\alpha = 0.025$, with 3 planned interim analyses. With the original planned sample size of 7800 patients per group, to be recruited within 2 years, and an average observation period of 4.5 years, a power of 93% will be achieved in the superiority setting, if the respective hazard ratio is 0.87; in the noninferiority setting, the power will be 89% if the respective hazard ratio is 1.00. For TRANSCEND, similar assumptions apply as for ONTARGET. With 3000 patients per group, a 94% power will be achieved for the alternative that the hazard ratio for telmisartan versus placebo is 0.81.

All analyses will be intention to treat and include all randomized patients. The primary analysis will be time to event, counting the first occurrence of any component of the composite outcome.³³ Secondary outcomes will be explored in a similar manner. Analyses for consistency of treatment effects in prespecified subgroups will be explored with respect to the primary and secondary outcomes by the Cox regression model, utilizing tests for interaction in order to examine the consistency of the results.³⁴ The prespecified subgroups are sex, age (<65 vs \geq 65 years), presence or absence of CV disease, DM, hypertension or microalbuminuria, and history of coronary artery disease, MI, cerebrovascular disease, or peripheral vascular disease.

Patient eligibility criteria

Included are patients with coronary artery, peripheral vascular, or cerebrovascular disease or high-risk DM with end-organ damage. Patients with known intolerance to ACE inhibitors are randomized to telmisartan or placebo in the TRANSCEND trial. Eligibility criteria are listed in Table II. Therefore, in general, physicians should be willing to randomize most patients to the ACE inhibitor ramipril, the ARB telmisartan, or their combination, and in TRANSCEND to telmisartan or placebo.

Run-in and randomization

Patients who fulfill the initial eligibility criteria enter (after written informed consent) a single blind "run-in" period (Table III); those who remain eligible are randomized via a 24-hour service computerized voice-activated telephone call to a central office in Hamilton, Ontario, Canada. After randomization, follow-up visits are made at 6 weeks, 6 months later, and then every 6 months until closeout. Figure 1 and Table III summarize the study schedule.

Table II. Patient eligibility criteria

Inclusion criteria	
Individuals \geq 55 years of age with 1 of the following	
Coronary artery disease	Previous myocardial infarction (>2 days post uncomplicated MI) Stable angina or unstable angina >30 days before informed consent and with documented evidence of multivessel coronary artery disease Multi-vessel PTCA >30 days before informed consent Multi-vessel CABG surgery >4 years before informed consent, or with recurrent angina following surgery
Peripheral artery disease	Previous limb bypass surgery or angioplasty Previous limb or foot amputation Intermittent claudication, with ankle:arm BP ratio \leq 0.80 on at least 1 side Significant peripheral artery stenosis (>50%) documented by angiography or non-invasive testing
Cerebrovascular disease	Previous stroke Transient ischemic attacks >7 days and <1 year before informed consent
Diabetes mellitus	High-risk diabetics with evidence of end-organ damage
Exclusion criteria	
Medication use	Inability to discontinue ACE inhibitors or ARB Known hypersensitivity or intolerance to ACE inhibitors or ARB (patient intolerant of ACE inhibitor can be enrolled in TRANSCEND)
Cardiovascular disease	Symptomatic congestive heart failure Hemodynamically significant primary valvular or outflow tract obstruction Constrictive pericarditis Complex congenital heart disease Syncope episodes of unknown etiology <3 months before informed consent Planned cardiac surgery or PTCA <3 months of informed consent Uncontrolled hypertension on treatment (eg, BP >160/100 mm Hg) Heart transplant recipient
Other conditions	Stroke due to subarachnoid hemorrhage Significant renal artery disease Proteinuria (TRANSCEND only) Hepatic dysfunction Uncorrected volume or sodium depletion Primary hyperaldosteronism Hereditary fructose intolerance Other major noncardiac illness expected to reduce life expectancy or interfere with study participation Simultaneously taking another experimental drug Significant disability precluding regular follow-up visits Unable or unwilling to provide written informed consent

Table III. Study summary

Identification and invitation	Identify eligible patients and invite patient to participate and send patient information pamphlet if needed
Eligibility and run-in visit (week 3)	Check patient eligibility (see Table II) Obtain informed consent Conduct physical examination Check urine using dipstick (exclude from TRANSCEND if proteinuria $\geq 1+$) Collect blood and urine samples for local and central laboratory testing and arrange for a serum potassium and creatinine measurement during final week of run-in Complete Run-in CRF Dispense run-in medications (single blind) as follows: ONTARGET Ramipril 2.5 mg + matching telmisartan placebo 40 mg for 3 days, then Ramipril 2.5 mg + telmisartan 40 mg for 7 days, then Ramipril 5 mg + telmisartan 40 mg for 11 to 18 days TRANSCEND
Randomization visit (week 0)	Telmisartan placebo 80 mg for 1 week, followed by telmisartan 80 mg daily for 2 to 3 weeks Check compliance with run-in drugs and confirm eligibility Obtain ECG and perform MMSE and other assessment as required Arrange for blood collection for local and central laboratory testing where required Arrange for a serum potassium and creatinine measurement during fifth week of randomization Phone AreS for patient randomization and dispense allocated study medication from study kit ONTARGET First 2 weeks: telmisartan 80 mg + ramipril placebo 5 mg OR ramipril 5 mg + telmisartan placebo 80 mg, OR telmisartan 80 mg + ramipril 5 mg Remainder of trial: telmisartan 80 mg + ramipril placebo 10 mg OR ramipril 10 mg + telmisartan placebo 80 mg OR telmisartan 80 mg + ramipril 10 mg TRANSCEND
Follow-up (at 6 weeks, 6 months, and then every 6 months until planned close-out in July 2007)	Telmisartan 80 mg OR placebo 80 mg for duration of trial Complete and datafax CRF for randomization visit Make follow-up appointment for 6 weeks (± 1 week) Check for all cardiovascular events and all hospitalizations Arrange for ECG, other assessments, local and central blood and urine tests as required Dispense study medications and encourage compliance Arrange for next follow-up visit (± 1 month) Complete follow-up CRF, and, as needed any hospitalization and events reports to Project Office Mail discharge summaries, laboratory results/reports, chest X-ray reports, ECG, CT scans etc in the ONTARGET/TRANSCEND envelope when requested

Study organization

In order to randomize 28,400 patients rapidly, the study network includes over 700 centers from 40 countries, with leadership provided through national coordinators. The trials are coordinated by the Population Health Research Institute (PHRI), McMaster University, Hamilton, Canada; Oxford University, United Kingdom; and University of Auckland, New Zealand. The overall responsibility for the conduct of the trials lies with the Steering Committee (see Appendix). An Operations Committee, with representatives from the PHRI Project Office, the Regional Coordinating Centers, and the sponsor, meets regularly.

Standardization and monitoring of data quality

Study staff underwent training sessions and site visits to ensure uniform procedures. A 24-hour toll-free telephone number is available to address any questions

related to study procedures. A manual of operations provides a detailed outline of the protocol. The case report forms (CRFs) are simple and easy to follow, with instructions printed on the reverse sides.

Data forms are optically read by DataFax system (Clinical DataFax Systems, Hamilton, Ontario, Canada) with accuracy and speed sufficient to allow routine monitoring of recruitment rates, patient schedules, and medication reordering. The original forms are faxed to the project office on toll-free numbers within 3 days of patient visits. Project Office staff verify the computer-read data. Queries and quality control reports are faxed to the investigator within 2 weeks.

Central event adjudication

Primary study outcomes are adjudicated by a central adjudicator at the Project Office, using essential infor-

mation supporting the diagnoses (eg, electrocardiographic and cardiac enzyme results for MI or computed tomography scans for strokes). Additional information may be requested. If there is full agreement between the central adjudicator and the clinical center, the event will be confirmed. If there is still disagreement, the events will be reviewed by the Events Adjudication Committee. A random 10% of the events confirmed by the central adjudicator will be reviewed by the Events Adjudication Committee. All unrefuted events will be included in the analysis.

Serious adverse events and unblinding

All serious events, including primary, secondary, and other study outcomes in the randomized period, are reported to the Project Office. Those judged to be serious, related to the study medications, and unexpected are expeditiously reported to the study sponsor for reporting to the regulatory authorities, where required. All serious adverse events are tabulated and reviewed periodically by the independent Data and Safety Monitoring Board. Central emergency unblinding is available when necessary by a telephone call to the Project Office.

Ethics and patient confidentiality

The protocol has been approved by regulatory authorities and the ethics review committees of local participating institutions in all countries. All patients provide written informed consent. Their confidentiality is protected.

Interim analysis and data monitoring

The independent Data Safety and Monitoring Board meets twice yearly; 3 formal interim analyses are planned, when 25%, 50%, and 75% of the events have been collected. A modification of the Haybittle-Peto approach³⁵ will be used to guide in decisions regarding early termination. This modification utilizes a boundary of 4 SD in the first half of the trials and 3 SD in the second half as a guide to efficacy. For safety, the respective boundaries are at 3 and 2 SD. Additionally, the boundary should remain crossed on 2 consecutive looks, 4 to 6 months apart.

Trial progress and baseline characteristics

Patients have been recruited from 730 centers in 40 countries. Recruitment into ONTARGET closed in July 2003. As of May 10, 2004, 25,620 patients have been randomized into ONTARGET and 5776 into TRANSCEND; recruitment will be completed by May 2004. Table IV shows the key patient baseline characteristics in each of the trials compared to the HOPE trial. In

Table IV. Key baseline characteristics (as of May 10, 2004)

Variable	ONTARGET	TRANSCEND	HOPE
No.	25,620	5776	9,541
Age (y)	66.4	66.9	65.9
Male (%)	73.3	57.1	73.3
History (%)			
MI	48.7	46.2	52.8
Stable angina	34.8	36.9	55.8
Unstable angina	14.8	14.9	25.7
CABG	22.1	18.9	26.0
PTCA/PCI	28.9	26.0	18.0
Stroke/TIA	20.7	22.1	10.8
Carotid endarterectomy	2.8	1.8	2.7
Peripheral artery surgery	5.8	4.2	6.2
Intermittent claudication	11.8	10.1	15.9
Risk factors (%)			
Hypertension	68.3	75.9	46.5
DM	37.3	35.4	38.3
Smoking			
Current	12.5	9.8	14.1
Former	51.9	43.4	57.1
Medications (%)			
ACE inhibitors	57.5	58.1	11.6
Angiotensin II blockers	8.6	29.9	–
β-Blockers	56.9	57.9	39.5
Diuretics	27.9	32.9	15.1
Nitrates	29.2	33.9	31.1
Diltiazem/verapamil	9.7	9.9	27.1
Other calcium-channel blockers	23.8	31.2	20.5
ASA	75.6	74.7	73.6
Ticlopidine	2.5	2.6	4.8
Clopidogrel	8.5	8.1	–
Oral anticoagulants	7.6	7.1	3.8
Statins	60.7	54.5	28.9
Insulin	10.4	7.2	11.7
Oral hypoglycemics	25.0	23.8	21.8
Estrogen (in females)	8.2	7.2	10.8
Estrogen + progesterone (in females)	2.2	2.1	2.6
Physical exam			
Heart rate (beats/min)	67.9	68.8	68.6
BP at run-in (mm Hg)	143/82	142/82	139/79
BP at randomization (mm Hg)	134/77	135/78	–
BMI	28.2	28.3	27.7
Waist-hip ratio	0.9	0.9	0.9
Laboratory results			
Creatinine (μmol/L)	94.3	92.6	96.9
Potassium (mmol/L)	4.4	4.4	4.4
Total cholesterol (mmol/L)	4.9	5.1	–
HDL-cholesterol (mmol/L)	1.3	1.3	–
LDL-cholesterol (mmol/L)	2.9	3.0	–
Triglycerides (mmol/L)	1.7	1.8	–

general, patient characteristics are generally similar to HOPE except that the current trials have greater ethnic diversity (as a result of inclusion of Asian countries), individuals are slightly older, and the proportion of patients with cerebrovascular disease is higher com-

pared to HOPE. In TRANSCEND, the proportion of women is higher than in ONTARGET or HOPE. The use of antiplatelet agents is similar, but the use of therapies known to reduce mortality/morbidity such as β -blockers or lipid-lowering therapy is higher in the current trials. The mean BP at run-in was 143/82 mm Hg and at randomization was 134/77 mm Hg in ONTARGET; in TRANSCEND, it was 142/82 and 135/78, respectively (note that in a proportion of patients, an ACE inhibitor or ARB was stopped at the beginning of run-in). These values are similar to the entry BP of 139/79 mmHg in HOPE.

Discussion

The use of 2 parallel trials in this program will reliably assess the comparative effects of an ARB, telmisartan, under a number of different circumstances. The effects of an ARB can be assessed in 2 ways. One way is to compare telmisartan versus ramipril in patients with proven indications for an ACE inhibitor, as it would be unethical to withhold an ACE inhibitor (or a potentially similar agent). This is an indirect assessment of efficacy and depends on the assumptions that (1) the circumstances of the current trial are similar to previous trials that documented the value of ACE inhibitors ("constancy"), and (2) the design of the study is able to detect differences ("sensitivity"). There are advantages in using a noninferiority design, but when using such a design to compare telmisartan with ramipril, their relative efficacy can only be assessed to a limited extent (because of the width of the CI) unless extremely large trials are carried out (or telmisartan is found to be superior). Even with this trial, which is designed to ensure that at least 50% of the benefits of ramipril versus placebo are preserved assuming that both treatments are identical, a sample size of 7800 per group (or 15,600 for a 2-arm trial) is needed. This is nearly 1.5 times the size of a trial comparing ramipril versus placebo or telmisartan versus placebo to detect a relative risk reduction of about 20%. If 80% of the benefits of ramipril versus placebo had to be guaranteed (which would translate into a noninferiority margin of 1.052), then the group size would have to be around 46,000 patients. Such studies are currently not practicable.

An alternative method of evaluating whether telmisartan is better than placebo is to test this question in individuals in whom ACE inhibitors cannot be used but who are otherwise similar. Thus, by conducting a parallel trial with an identical design on those patients who are ACE-inhibitor intolerant, a direct evaluation of telmisartan versus placebo is possible. A positive outcome of this trial would also confirm the sensitivity of the design, thereby confirming a potential noninferiority claim of telmisartan versus ramipril. However, we

have to assume that ACE-inhibitor intolerance is unrelated to responsiveness to ARBs, an assumption that can only be validated at the end of the study. Therefore, by conducting the 2 parallel studies, a range of complementary information on the relative efficacy and safety of each of 2 drugs and their combination can be obtained.

As designed, the baseline characteristics of patients in the trials are comparable to those in the HOPE study,⁶ with patients who are at high risk and have a BP in the "normal" range. A high proportion of the patients are receiving other drugs that could lower BP, although a significant proportion of these are for secondary prevention rather than BP control. Therefore, we will be evaluating the effects of telmisartan over and above good BP control and in addition to other treatments. Additionally, 76% patients receive aspirin and 60% lipid-lowering medications (statin), a relatively high rate of use of therapies with proven efficacy.

In addition to evaluating the effects of telmisartan and ramipril on the CVD outcomes, there are a number of other outcomes that are novel, including effects on atrial fibrillation and cognitive decline. The 7 sub-studies embedded in the main trials are designed to obtain insights into mechanisms of the effects of the drugs, and additional benefit of treatments (eg, on erectile dysfunction). The stored blood samples can provide unique material for the study of cardiovascular epidemiology and the impact of a range of biological markers on CVD. Since the trials are being conducted in 40 countries involving all the inhabited continents of the world, they will provide a unique opportunity to examine the practice patterns and the epidemiology of chronic diseases in a large diverse group of individuals.

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