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The Prevention of Cerebrovascular and Cardiovascular Events of Ischemic Origin with Terutroban in Patients with a History of Ischemic Stroke or Transient Ischemic Attack (PERFORM) Study: Baseline Characteristics of the Population

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Key Words
Antiplatelet therapy · Aspirin · Ischemic stroke · PERFORM Study · Transient ischemic attack · Terutroban · TP receptor antagonist · Stroke prevention

Abstract
Background: The Prevention of cerebrovascular and cardiovascular Events of ischemic origin with teRutroban in patients with a history oF ischemic strOke or tRansient ischeMic attack (PERFORM) study is an international double-blind, randomized controlled trial designed to investigate the superiority of the specific TP receptor antagonist terutroban (30 mg/day) over aspirin (100 mg/day), in reducing cerebrovascular and cardiovascular events in patients with a recent history of ischemic stroke or transient ischemic attack. Here we describe the baseline characteristics of the population. ***Methods and Results:*** Parameters recorded at baseline included vital signs, risk factors, medical history, and concomitant treatments, as well as stroke subtype, stroke-associated disability on the modified Rankin scale, and scores on scales for cognitive function and dependency. Eight hundred and two centers in 46 countries recruited a total of 19,119 patients between February 2006 and April 2008. The population is evenly distributed and is not dominated by any one country or region. The mean ± SD age was 67.2 ± 7.9 years, 63% were male, and 83% Caucasian; 83% had hypertension, and about half the population smoked or had quit smoking. Ninety percent of the qualifying events were ischemic stroke, 67% of which were classified as atherothrombotic or likely atherothrombotic (pure or coexisting with another cause). Modified Rankin scale scores showed slight or no disability in 83% of the population, while the scores on the Mini-Mental State Examination, Isaacs' Set Test, Zazzo's Cancellation Test, and the instrumental activities of daily living scale showed a good level of cognitive function and autonomy. ***Conclusions:*** The PERFORM study population is homogeneous in terms of demographic and disease characteristics. With 19,119 patients, the PERFORM study is powered to test the superiority of terutroban over aspirin in the secondary prevention of cerebrovascular and cardiovascular events in patients with a recent history of ischemic stroke or transient ischemic attack.

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Introduction

Ischemic stroke accounts for approximately 87% of all strokes and is the second largest cause of mortality worldwide [1, 2]. Major advances in the prevention of recurrent ischemic stroke have occurred over the past 30 years, and current strategies include the aggressive management of hypertension, hypercholesterolemia, and diabetes mellitus, smoking cessation and reduction in body mass index, and prophylactic administration of antiplatelet agents [3]. Aspirin remains the most widely prescribed antiplatelet agent for secondary prevention of ischemic stroke, despite its gastrointestinal toxicity [4]. Other antiplatelet agents, most notably extended-release dipyridamole combined with aspirin, ticlopidine, and clopidogrel, are slightly more effective than aspirin.

Terutroban is a specific TP receptor antagonist, i.e. an antagonist of the receptors for thromboxane A_2 and prostaglandin endoperoxide (PGG_2-PGH_2). Terutroban is an antithrombotic agent at least as effective as aspirin in inhibiting platelet aggregation [5], superior to aspirin alone and similar to aspirin/clopidogrel combination in inhibiting thrombus formation in a population at risk of stroke [6]. Aside from being an antithrombotic agent, terutroban also has vascular properties, i.e. antivasoconstrictive property by improving endothelial function [7], antiatherosclerotic property by inhibiting vessel wall proliferation [8], as well as antioxidant [9] and anti-inflammatory [10] properties, which could contribute to its therapeutic potential. Preclinical and clinical studies indicated a good safety profile of terutroban. The efficacy and safety of oral terutroban in secondary prevention in patients with ischemic stroke is currently being evaluated in the Prevention of cerebrovascular and cardiovascular Events of ischemic origin with teRutroban in patients with a history oF ischemic strOke or tRansient ischeMic attack (PERFORM) study.

The PERFORM study is an international trial aiming to demonstrate the superiority of terutroban (30 mg/day) over aspirin (100 mg/day), in reducing cerebrovascular and cardiovascular events in patients with a recent history of ischemic stroke or transient ischemic attack (TIA). The worldwide recruitment for the PERFORM study is now complete and, in this article, we describe the baseline characteristics of this study population.

Methods

The PERFORM study is a double-blind, randomized, parallel-group trial carried out in 802 centers in 46 countries. The study design has been described in depth elsewhere [11]. Briefly, male and female patients aged ≥55 years were eligible for inclusion if they had suffered an ischemic stroke or a retinal infarction of arterial origin in the previous 3 months, or a TIA in the previous 8 days. Participants had to be neurologically, clinically, and hemodynamically stable, and had to have a CT scan or MRI ruling out intracranial hemorrhage or any nonischemic neurological disease. All patients gave written informed consent. The PERFORM trial is registered on www.controlled-trials.com (ISRCTN-66157730).

Patients were randomly allocated to treatment with either terutroban (30 mg/day) or aspirin (100 mg/day). At baseline (month 0, randomization), the parameters recorded for each participant included vital signs (blood pressure, heart rate, weight and height), risk factors (age, ethnicity, and smoking status), medical history, and concomitant treatments. The results of CT scan or MRI were evaluated for the diagnosis of stroke or TIA, and the qualifying event was categorized according to a predefined classification of ischemic stroke [11]. Stroke-associated disability was assessed on the modified Rankin scale [12]. Cognitive function was also evaluated at baseline (month 1) using scores on the Mini-Mental State Examination (MMSE) [13], Isaacs' Set Test (IST) [14], Zazzo's Cancellation Test (ZCT) [15], and the instrumental activities of daily living scale (IADL) [16].

The primary endpoint of the PERFORM study is a composite of fatal or nonfatal ischemic stroke, fatal or nonfatal myocardial infarction, and other vascular death (excluding hemorrhagic death of any origin).

The baseline data are presented as means ± SD or counts and/or percentages, as appropriate.

Results

Recruitment into the PERFORM study started on February 22, 2006 and the last patient was randomized on April 7, 2008: 19,119 patients were randomized from 802 centers in 46 countries. The geographic distribution of the PERFORM study population at baseline is presented in table 1. Forty percent of the population were recruited in Western Europe, 32% in Eastern and Central Europe, 11% in Asia, 9% in South America and 3, 3, and 2% in Oceania, Canada, and Africa, respectively.

Demographic characteristics and past medical history are presented in table 2. The mean age of the population was 67.2 ± 7.9 years (minimum 54 years, maximum 98 years), with 20% of patients over 75 years. Sixty-three percent of the population was male and 83% of Caucasian origin. The most frequent risk factors were hypertension (83%), hypercholesterolemia (48%), and diabetes (28%). Fourteen percent of the population reported a previous ischemic stroke and 7% a previous TIA, while 8% had a

Table 1. Geographical distribution of the PERFORM study population by country and region

Country	Centers	Patients
Western Europe		
Austria	16	189
Belgium	22	563
Finland	9	245
France	56	796
Germany	66	1,480
Greece	5	29
Ireland	6	25
Italy	61	1,098
Luxembourg	1	17
Norway	5	99
Portugal	6	262
Spain	53	1,077
Sweden	8	128
Switzerland	9	204
The Netherlands	19	467
The UK	52	865
Turkey	10	78
Eastern Europe		
Bulgaria	10	467
Croatia	6	190
Czech Republic	10	787
Hungary	22	766
Lithuania	6	193
Poland	24	384
Romania	15	809
Russia	56	1,594
Slovakia	14	533
Slovenia	4	157
Ukraine	7	213
North America		
Canada	32	483
South America		
Argentina	23	463
Brazil	22	1,021
Chile	11	165
Mexico	12	119
Asia		
China	21	468
Hong Kong	4	224
India	14	277
Malaysia	2	61
Singapore	3	173
South Korea	11	377
Taiwan	8	255
Thailand	8	343
Oceania		
Australia	24	494
New Zealand	7	83
Africa		
Morocco	5	117
South Africa	10	130
Tunisia	7	151
Total PERFORM study	802	19,119

Table 2. Baseline characteristics of the PERFORM study population

Total patients	19,119
Male, %	63
Mean age, years	67.2 ± 7.9
Age, %	
<65 years	41
≥65 to <75 years	39
≥75 years	20
Ethnicity, %	
Caucasian	83
Asian	12
Black	2
Other	3
Physical examination	
Body mass index, kg/m^2	27.1 ± 4.3
Systolic blood pressure, mm Hg	137 ± 16
Diastolic blood pressure, mm Hg	80 ± 9
Heart rate, bpm	71 ± 10
Smoking, %	
Never smoked	49
Current smoker	26
Stopped smoking >6 months	25
Medical history, %	
Hypertension	83
Hypercholesterolemia	48
Diabetes	28
Prior history of cerebral infarction	14
Angina pectoris	10
Hypertriglyceridemia	9
Prior history of TIA	7
Myocardial infarction	8
Peripheral artery disease	4
Previous treatments[1], %	
Statins	60
Angiotensin-converting enzyme inhibitors	55
Diuretics	36
Calcium channel blockers	28
β-Blockers	27
Antidiabetic drugs	23
Angiotension II receptor blockers	10
Antiplatelet agents at baseline[1], %	
Aspirin	88
Dipyridamole	10
Clopidogrel	8
Aspirin + dipyridamole	5
Ticlopidine	1

Data are presented as means ± SD, counts, or percentages.
[1] Recorded between index stroke and randomization.

Table 3. Qualifying event and stroke characteristics of the PERFORM study population

Qualifying event, %	
Ischemic stroke	90
TIA	10
Arterial retinal ischemic event	0.4
Mean delay between qualifying event and randomization, days	
Ischemic stroke	26.9 ± 24.0
TIA	5.8 ± 5.4
Arterial retinal ischemic event	34.3 ± 26.9
Delay between qualifying event and randomization, %	
≤1 week	26
>1 week to ≤1 month	46
>1 month	28
Ischemic stroke subtypes, %	
Atherothrombotic stroke[1]	11
Likely atherothrombotic stroke[1]	42
Cardioembolic stroke[1]	1
Lacunar stroke[1]	10
Coexisting	15
Unknown cause	21
Modified Rankin scale, %	
Class 0	22
Class 1	38
Class 2	23
Class 3	11
Class 4	6
MMSE[2], score (n = 18,325)[3]	27.6 ± 3.2
MMSE[2], %	
Score <15	0.8
Score 15–18	1.5
Score 19–22	5
Score ≥23	92.7
IST[2], score (n = 18,778)[3]	31.7 ± 6.5
IST[2], %	
Score <20	5
Score 20–28	24
Score ≥29	71
ZCT[2], score (n = 18,548)[3]	26.9 ± 4.0
ZCT[2], %	
Score <11	1.5
Score 11–19	3.5
Score >19	95
IADL[2], score (n = 18,891)[3]	3.6 ± 0.8
IADL[2], %	
Score 0–1	5
Score 2–3	16
Score 4	79

[1] Subtype without coexisting cause.
[2] Recorded at 1 month.
[3] Number of patients with test results available.

history of myocardial infarction. At baseline, after the qualifying stroke, 88% of the patients were receiving aspirin, 60% a statin, and 55% an angiotensin-converting enzyme inhibitor. Mean blood pressure was 137/80 mm Hg.

Data relative to the qualifying event and disease characteristics are presented in table 3. Ninety percent of qualifying events were ischemic stroke with a mean delay from the qualifying event to randomization of 27 days. Seventy-two percent of the population were included within 1 month of the qualifying event. According to the prespecified ischemic stroke classification, pure atherothrombotic or likely atherothrombotic stroke represents 53% of the ischemic stroke population, and 10% had pure lacunar stroke. Dual causes represent 15% of the population, which includes 13% lacunar strokes combined with other subtypes (mainly likely atherothrombotic). Taken together, 23% of the population had a lacunar stroke, and 67% had an atherothrombotic or likely atherothrombotic stroke.

According to the modified Rankin scale scores at baseline (table 3), 83% of the patients had scores ≤2, indicative of no or slight disability. One of the inclusion criteria was the absence of dementia at baseline. Accordingly, at baseline, 93% of the population had an MMSE score ≥23, 71% had a score ≥29 on the IST for verbal fluency, and 95% had a score >19 on the ZCT for selective attention. The level of dependency, as evaluated by the IADL scale, scored 4 for 79% of the population.

Discussion

At the time the enrolment of the PERFORM study was closed, 19,119 patients with a history of stroke or TIA had been randomized. The geographical distribution of the PERFORM study population is extremely broad covering 802 centers in 46 countries on 6 continents. This avoids domination of any one particular country or region. Moreover, although the PERFORM study included a primarily Caucasian population, the sheer scale of the study means that ethnic groups such as Asians reach sizable representations (>2,000 participants). The size of the PERFORM trial allows the direct comparison of terutroban and aspirin, and the study should have reasonable power to identify subgroups of patients who will benefit from terutroban.

The mean age of patients (67 years) and the preponderance of males are in accordance with other recent trials of secondary prevention such as the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL),

Table 4. Comparison of baseline characteristics of patients in three recent major trials of secondary prevention (SPARCL, MATCH, and PRoFESS) and PERFORM

	SPARCL [17, 18]	MATCH [19]	PRoFESS [20]	PERFORM
Number of patients	4,732	7,599	20,333	19,119
Age, years	62.8 (range, 21–92)	66.3 ± 9.9	66.1 ± 8.6	67.2 ± 7.9
Sex, % male	60	63	64	63
Mean blood pressure, mm Hg	139/82	NA	144/84	137/80
Qualifying event				
Time from qualifying event to randomization, days	≤30	27	15	27
Ischemic stroke, %	67	78	100	90
TIA, %	31	22	0	10
Large-vessel disease, %	15.8	34	29	67
Small-vessel disease, %	29.8	53	52	23
Concomitant treatments				
Angiotensin-converting enzyme inhibitor, %	29	52	37	55
Statin, %	3	36	47	60
Medical history				
Hypertension, %	60	78	74	83
Diabetes, %	16	68	28	28
Prior ischemic stroke, %	15	26	18	14
Prior TIA, %	19	19	9	7

NA = Not available.

the Management of Atherothrombosis with Clopidogrel in High-Risk Patients with Recent Transient Ischaemic Attack or Ischaemic Stroke (MATCH), and the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) (table 4) [17–20], and are reasonably consistent with data from hospital registries and stroke incidence studies [21–23]. As the recurrence of stroke is highest during the first month after the first event, the investigators were encouraged to enroll patients as early as possible, once they were stabilized. Seventy-two percent of patients with an ischemic stroke were randomized within the first month, including 26% in the first week, which compares well with 70% of patients in the PRoFESS study, also randomized in the first month.

In contrast to the PRoFESS and MATCH trials, which included a large proportion of patients with small-vessel disease (>50%), the PERFORM study, on the basis of the antiatherosclerotic properties of terutroban, deliberately enrolled a majority (67%) of patients with large-vessel disease (atherothrombotic or likely atherothrombotic stroke) and fewer patients with small-vessel disease (lacunar stroke, 23%). The proportion of small- and large-vessel disease strokes in the PERFORM study is more representative of the general stroke population, as only one third of ischemic strokes of noncardioembolic origin are lacunar [24].

In terms of risk factors, the PERFORM study population is representative of the general stroke population, with a majority of hypertensive patients (83% vs. 74% in PRoFESS and 78% in MATCH), though mean blood pressure at baseline was well controlled (137/80 mm Hg). Diabetes was present in 28% of patients versus 28% in PRoFESS and 68% in MATCH. Finally, the use of guideline-recommended medical treatment in the PERFORM study at baseline was high, with 55% of patients receiving an angiotensin-converting enzyme inhibitor and 60% a statin.

Conclusion

With over 19,000 participants from all major continents, the PERFORM study is the largest ongoing study in ischemic stroke. The recruitment has produced a representative population in terms of both demographic and disease characteristics. The PERFORM study can be expected to provide important data on the benefit of terutroban 30 mg/day compared with aspirin 100 mg/day in reducing cerebrovascular and cardiovascular events, in patients with a noncardioembolic ischemic stroke or a TIA. The results are expected in 2011.

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Conflict of Interest Statement

The authors have all received honoraria, research grants, or both from Servier.

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