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Rationale and Design of a Randomized, Double-Blind, Parallel-Group Study of Terutroban 30 mg/day versus Aspirin 100 mg/day in Stroke Patients: 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

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

Abstract
Background: Ischemic stroke is the leading cause of mortality worldwide and a major contributor to neurological disability and dementia. Terutroban is a specific TP receptor antagonist with antithrombotic, antivasoconstrictive, and antiatherosclerotic properties, which may be of interest for the secondary prevention of ischemic stroke. This article describes the rationale and design of 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, which aims to demonstrate the superiority of the efficacy of terutroban versus aspirin in secondary prevention of cerebrovascular and cardiovascular events. ***Methods and Results:*** The PERFORM Study is a multicenter, randomized, double-blind, parallel-group study being carried out in 802 centers in 46 countries. The study population includes patients aged ≥55 years, having suffered an ischemic stroke (≤3 months) or a transient ischemic attack (≤8 days). Participants are randomly allocated to terutroban (30 mg/day) or aspirin (100 mg/day). The primary efficacy endpoint is a composite of ischemic stroke (fatal or nonfatal), myocardial infarction (fatal or nonfatal), or other vascular death (excluding hemorrhagic death of any origin). Safety is being evaluated by assessing hemorrhagic events. Follow-up is expected to last for 2–4 years. Assuming a relative risk reduction of 13%, the expected number of primary events is 2,340. To obtain statistical power of 90%, this requires inclusion of at least 18,000

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patients in this event-driven trial. The first patient was randomized in February 2006. ***Conclusions:*** The PERFORM Study will explore the benefits and safety of terutroban in secondary cardiovascular prevention after a cerebral ischemic event.
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Introduction

Stroke is the leading cause of death worldwide [1, 2], and a major cause of acquired disability. By contrast with the declining incidence of coronary heart disease [3–5], current projections indicate an increase in stroke incidence and prevalence in the coming decades, with two thirds of deaths secondary to cerebrovascular disease occurring in the developing world [1]. Thus, the numbers of first-ever strokes and stroke deaths, which were, respectively, 16 and 5.7 million worldwide in 2005, are expected to rise to 23 and 7.8 million by 2030 [6].

Ischemic stroke accounts for about 85% of all strokes, and patients who survive are at a particularly high risk for subsequent cardiovascular events (5-year rate, 24% [7]), including recurrent stroke, myocardial infarction, and death from vascular causes. Furthermore, approximately 30% of survivors meet criteria for post-stroke dementia [8], and it is well established that cerebrovascular disease and Alzheimer's disease often occur together and may potentiate each other [9]. Prevention is thus crucial to reduce the burden of stroke and vascular dementia [10].

Secondary prevention of ischemic stroke is based on the treatment of vascular risk factors, including antihypertensive therapy, lipid-lowering agents, and smoking cessation, and on the use of oral antithrombotic agents, i.e., oral anticoagulants in cardioembolic diseases and antiplatelet drugs in arterial disease. In the large Antithrombotic Trialists' Collaboration meta-analysis [11], antiplatelet agents reduced the combined risk of stroke, myocardial infarction, and vascular death after transient ischemic attack (TIA) or ischemic stroke by 22%. Aspirin has been the most widely studied antiplatelet agent and remains the most widely used, though both clopidogrel [12] and the combination of aspirin and extended-release dipyridamole [13] have been found to be slightly but significantly more effective than aspirin. By contrast, the combination of clopidogrel and aspirin has no proven benefit over clopidogrel alone after a cerebral ischemic event [14], and more potent antiplatelet drugs, such as GP IIb/IIIa antagonists, have failed due to increased rates of hemorrhage and mortality [15].

Rationale

Terutroban is an antiplatelet drug that is at least as effective as aspirin [16]. It also has antiatherosclerotic and antivasoconstrictive properties that might be of benefit in the prevention of ischemic stroke. It is a specific antagonist of the receptors for thromboxane A_2 (TXA_2) and prostaglandin endoperoxide (PGG_2-PGH_2). These so-called TP receptors are membrane-bound G protein-coupled receptors, found in many cell types, including platelets, vascular cells, and monocytes/macrophages [17]. Terutroban selectively inhibits TP receptors in platelets and in the vessel wall, and therefore inhibits platelet aggregation and prevents vascular dysfunction. In contrast to aspirin, the effect of terutroban is reversible; terutroban does not inhibit constitutive or inducible cyclooxygenase (COX-1 and COX-2, respectively), or any pathway of prostanoid synthesis, which means that prostacyclin-dependent vasodilation is preserved. In addition, terutroban inhibits the platelet and vascular action of TXA_2 released from extraplatelet sources, such as monocyte COX-2, as well as that of other eicosanoids [18], which are insensitive to aspirin [19] and whose production is increased in atherosclerosis. In this respect, there is strong evidence that terutroban inhibits the development of atherosclerotic lesions by a mechanism independent of platelet TXA_2 production, most likely due to the inhibition of the effect of eicosanoids of extraplatelet origin, such as isoprostanes [18, 20].

Animal studies have shown that terutroban has beneficial effects on platelet aggregation, thrombus formation, vascular reactivity, and vessel wall proliferation [21–23]. In rabbits, it reduces the size of atherosclerotic plaque, intima-media thickness, intracellular adhesion molecule expression in endothelial cells, and monocyte/macrophage infiltration in the vessel walls [24].

The inhibition of platelet aggregation by oral administration of terutroban has been confirmed in pharmacokinetic and pharmacodynamic studies in humans [25]. It appears to be at least as effective as aspirin, with a rapid ($\leq$1 h) and dose-dependent duration of action, dose-dependent reversibility (24–96 h), and an increase in bleeding time similar to that of aspirin [25]. Terutroban has been found to improve endothelial function as assessed by forearm vascular reactivity in patients with carotid artery stenosis on top of treatment with aspirin [26]. In a pilot study based on an ex vivo model of thrombosis in patients undergoing treatment for the secondary prevention of stroke, terutroban had an antithrombotic effect superior to that of aspirin alone and similar to that of an

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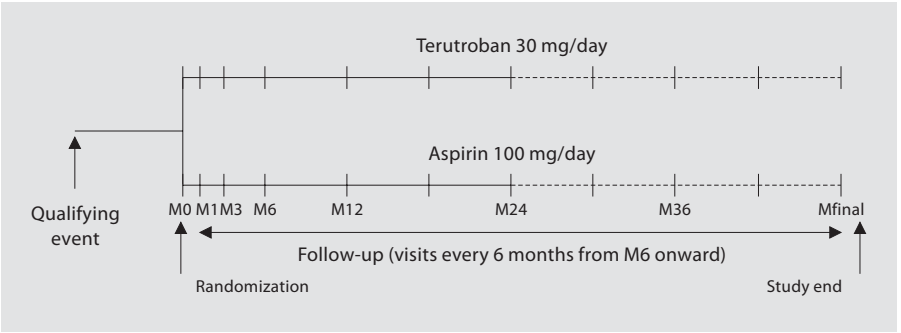

Fig. 1. Design of the PERFORM Study. M = Month.

aspirin/clopidogrel combination [27]. Theoretically, terutroban could prove to have additional clinical benefits due to its antioxidant [28] and anti-inflammatory [29] properties, its effect on endothelial dysfunction, and its ability to reduce amyloid deposits in animal models of Alzheimer's disease [30].

The aim of 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 therefore to demonstrate the superiority of terutroban (30 mg/day) versus aspirin (100 mg/day), in reducing cerebrovascular and cardiovascular events in patients with a history of ischemic stroke or TIA.

Study Design

The PERFORM Study is an international, multicenter, randomized, double-blind, parallel-group study being carried out in 802 centers in 46 countries. The study design is presented in figure 1, and the inclusion criteria and major exclusion criteria are shown in table 1. In brief, male and female patients aged ≥55 years were included if they had a cerebral or retinal infarction of arterial origin in the 3 months preceding inclusion, or a TIA in the previous 8 days. Ischemic stroke was defined as a focal ischemic neurological deficit lasting ≥24 h, or lasting less than this but with computed tomography (CT) scan or magnetic resonance imaging (MRI) evidence of corresponding cerebral infarction. TIA was defined as a focal ischemic neurological deficit including at least weakness in the limbs and/or aphasia, and lasting <24 h, in the absence of CT scan or MRI evidence of corresponding cerebral infarction. Ischemic stroke subtypes were categorized into six groups according to the classification presented in table 2.

Ethics and Informed Consent

The study is being performed in accordance with the ethical principles set out in the Declaration of Helsinki, 1964, as revised in Tokyo, 2004. The study protocol has been reviewed by independent ethics committees in the countries concerned, and by investigators, coordinators, or the sponsor in accordance with local regulations. Patients have been fully informed, and written consent has been obtained according to local regulatory requirements. The PERFORM Study is registered with www.controlled-trials.com (registration number ISRCTN66157730).

Treatment and Follow-Up

Baseline assessment is performed at the randomization visit. Patients are instructed to take one tablet daily of study treatment (30 mg/day terutroban or 100 mg/day aspirin) in the morning, starting the day after randomization. Treatment allocation is performed through a central interactive response system (telephone or internet) based on balanced, randomized, permuted blocks, and stratified by country. Patients and investigators are blinded to treatment allocation, and the study treatments have identical appearance. Background treatment may include all treatments not listed in the exclusion criteria, including ACE inhibitors and lipid-lowering agents. Patients are advised not to use aspirin as an analgesic during the study.

In addition to verification of the inclusion and exclusion criteria, medical history, and concomitant treatments, the following parameters are recorded at baseline (table 3): vital signs including blood pressure and heart rate; weight and height; results of CT scan or MRI performed for the diagnosis of stroke or TIA, and scores on

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Table 1. Inclusion and exclusion criteria for the PERFORM Study

Inclusion criteria
- Male or female
- Age at selection ≥55 years
- Patients having suffered an ischemic stroke or an arterial retinal ischemic event confirmed by an ophthalmologist >48 h and ≤3 months before randomization
- Patients having suffered a TIA ≤8 days before randomization
- Patients who are neurologically, clinically, and hemodynamically stable
- Patients with a CT scan or MRI ruling out intracranial hemorrhage or any nonischemic neurological disease
- Written informed consent obtained

Major exclusion criteria
- Patients with cognitive impairment, known dementia, or another condition that may interfere with the obtainment of informed consent and/or cooperation in the study
- Patients with:
  - Symptoms of TIA other than motor weakness in the limbs or aphasia and without CT scan or MRI evidence of an acute brain lesion
  - Modified Rankin scale score >4
  - Cerebral venous thrombosis
  - A cardiac source of embolism requiring prolonged treatment with vitamin K antagonists, such as prosthetic heart valve, mitral stenosis, atrial fibrillation, sick sinus syndrome, myocardial infarction within the prior 4 weeks, mural thrombus in left cavities, left ventricular aneurysm, dilated cardiomyopathy, intracardiac mass, or endocarditis
  - Acute stroke of another determined etiology or iatrogenic stroke
  - Carotid endarterectomy or angioplasty in the 30 days prior to randomization or planned within 6 months
  - Uncontrolled hypertension at the time of inclusion
- History of primary intracranial hemorrhage judged to be of sufficient severity to preclude initiation of an antiplatelet agent, hemorrhagic transformation of ischemic stroke, intracranial neoplasm, arteriovenous malformation, aneurysm or intracranial surgery, suspected dissection of the cervical and/or cerebral vessels or suspected aortic dissection, major surgery or trauma <6 weeks prior to randomization, or major surgery scheduled at the time of randomization, biopsy of a parenchymal organ <6 weeks prior to randomization, known hemostasis or coagulation disorder, known active or recent retinal hemorrhage or internal bleeding
- Patients with peptic ulcer, retinal hemorrhage or internal bleeding, or macroscopic hematuria <1 year prior to randomization
- History of aspirin-related hemorrhage or aspirin hypersensitivity
- Requiring, or likely to require, the following medications: fixed-combination aspirin/dipyridamole, triflusal, indobufen, cilostazol, or thienopyridines, vitamin K antagonists, full therapeutic dose of heparin, direct antithrombins, specific factor Xa antagonists, GP IIb/IIIa inhibitors, systemic steroidal and nonsteroidal anti-inflammatory drugs, including COX-2 inhibitors
- Patients having received fibrinolytics within the previous 48 h
- Patients with abnormal laboratory parameters: creatinine clearance <30 ml/min, ASAT or ALAT >3 × upper normal limit; platelets <120 G/l; hemoglobin <110 g/l (male) or <100 g/l (female)

Table 2. Classification of ischemic stroke subtype in the PERFORM Study

(1a) Atherothrombotic stroke
Patients with (1) an ipsilateral internal carotid stenosis >50% (in NASCET criteria), or (2) an ipsilateral stenosis >50% of another intra/extracranial artery, or (3) mobile thrombus in the aortic arch

(1b) Likely atherothrombotic stroke
Patients with no evidence of atherothrombotic stroke as defined in 1a with (1) an ipsilateral internal carotid stenosis <50%, or (2) an ipsilateral stenosis <50% of another intra/extracranial artery, or (3) aortic arch plaques >4 mm in thickness without a mobile component, or (4) a history of myocardial infarction or coronary revascularization, (5) a history of documented peripheral arterial disease, or (6) at least two risk factors for atherosclerotic disease: arterial hypertension (treated or known blood pressure before stroke >140/90 mm Hg or hypertensive retinopathy), diabetes mellitus (treated or known blood fasting glucose >7 mmol/dl), current smoking (or smoking stopped within the last 6 months), high cholesterol (treated or known low-density lipoprotein before the stroke >160 mg/dl)

(2) Cardioembolic stroke
Patients with mitral stenosis, prosthetic heart valve, myocardial infarction within the previous 4 weeks, mural thrombus in left cavities, left ventricular aneurysm, any history of (paroxysmal or permanent) atrial fibrillation or flutter with or without spontaneous echocontrast or left atrial thrombus, sick sinus syndrome, dilated cardiomyopathy, endocarditis, intracardiac mass

(3) Lacunar stroke
Patients with a small deep infarct measuring <15 mm on MRI (or CT) in the territory corresponding to symptoms, in a patient presenting a clinical syndrome compatible with a small deep infarct

(4) Rare causes
Patients who had rare causes, e.g. arterial dissection, polycythemia vera, thrombocythemia, lupus erythematosus

(5) Coexisting cause
Patients with two or more etiologies defined in 1–4

(6) Unknown cause
Patients who did not meet criteria for the groups as defined above, maybe with incidental findings (e.g. isolated elevation of antiphospholipid antibodies, patent foramen ovale, atrial septal aneurysm, valvular strands, mitral valve prolapse, mitral annulus calcifications, plaques in the aortic arch <4 mm in thickness and without mobile component)

NASCET = North American Symptomatic Carotid Endarterectomy Trial.

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Table 3. PERFORM investigation schedule

	Selection	M0	M1	M3	M6	M12	M18	M24	M30	M36	M42	M48 or final visit
Informed consent	X											
Inclusion/noninclusion criteria		X										
Medical history	X											
Vital signs		X	X	X	X	X	X	X	X	X	X	X
Weight		X				X		X		X		X
Height		X										
CT scan or MRI		X										
Concomitant treatments	X	X	X	X	X	X	X	X	X	X	X	X
Compliance					X	X	X	X	X	X	X	X
Efficacy assessments												
Efficacy on critical events		X	X	X	X	X	X	X	X	X	X	X
Modified Rankin scale	X	X	X	X	X	X	X	X	X	X	X	X
Barthel Index												X
IADL, MMSE, IST, ZCT		X	X		X	X		X		X		X
Additional cognitive evaluation[a]					(X)	(X)		(X)		(X)		(X)
Safety assessments												
Other medical events		X	X	X	X	X	X	X	X	X	X	X
Standard 12-lead ECG		X				X		X		X		X
Blood/urine sampling		X	X	X		X		X		X		X
Additional measurements												
Quality of Life questionnaires		X	X		X	X		X		X		X
Carotid ultrasonography		X				X		X		X		
Cerebral MRI			X					X				X
Blood samples for pharmacokinetics			X			X		X				
Blood/urine samples for biomarkers		X		X		X		X		X		X

ECG = Electrocardiogram. [a] In case of suspected cognitive decline or dementia.

the modified Rankin scale [31], Mini-Mental State Examination (MMSE) [32], Isaacs' Set Test (IST) [33] for verbal fluency, and Zazzo's Cancellation Test (ZCT) [34] for selective attention, and the instrumental activities of daily living (IADL) [35].

Follow-up visits are performed at 1, 3, and 6 months, and at 6-monthly intervals thereafter (fig. 1; table 3). The number of visits per participant depends on the duration of follow-up: minimum duration is 2 years, and the estimated mean duration is 3 years. Clinical examination is performed, and concomitant treatments are recorded at every visit. Compliance (by tablet counting) is evaluated at every 6-month visit. Cognitive function is evaluated at 1, 6, and 12 months, and yearly thereafter, using the MMSE, IST, and ZCT. Dependency is measured at the same visits using the IADL. Disability is assessed at the last visit using the Barthel Index [36].

Safety is evaluated at every visit, including hemorrhagic events (e.g. intracranial hemorrhage, gastrointestinal bleedings, and all other bleedings), gastrointestinal tolerability, and nonvascular death. All adverse events are reported and followed up completely. Electrocardiographic and laboratory parameters (hematology and biochemistry) are also recorded at 1 and 3 months, and at yearly intervals. Predefined events considered to be related to ischemic stroke or its complications, or the underlying atherothrombotic disease, are reported as endpoints. Patients who discontinue study treatment and do not formally withdraw consent will be followed up for the duration of the study.

Endpoints

The primary endpoint is a composite of fatal or nonfatal ischemic stroke, fatal or nonfatal myocardial infarction, or other vascular death (excluding hemorrhagic death of any origin). The secondary endpoints are listed

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Table 4. Primary and secondary efficacy endpoints

Primary endpoint	Composite of ischemic stroke (fatal or nonfatal), myocardial infarction (fatal or nonfatal), or other vascular death[a]
Secondary endpoints	Occurrence of: – Composite of any stroke (fatal or nonfatal), myocardial infarction (fatal or nonfatal), or other vascular death[a] – Ischemic stroke (fatal or nonfatal) – Myocardial infarction (fatal or nonfatal) – Other vascular death[a] – Nonfatal ischemic stroke – Fatal ischemic stroke – Nonfatal myocardial infarction – Fatal myocardial infarction – All-cause mortality – Any stroke (ischemic stroke or hemorrhagic stroke or unknown type, fatal or nonfatal) – Any fatal stroke – Disabling stroke Cognitive decline Dementia

[a] Excluding hemorrhagic death of any origin.

in table 4. All endpoints are documented on an ongoing basis. The following events, identified as critical events, are adjudicated by the blinded Critical Events Committee: all deaths, suspected strokes, TIA with available neuroimaging, myocardial ischemic events, heart failure or other cardiac events leading to hospitalization, and bleedings. Patients with suspected cognitive decline or dementia (based on a decrease of $\geq$3 points on the MMSE versus M1, or MMSE score <23, or IST score <20, or in the opinion of the investigator) are referred for specific evaluation by a dementia specialist at the earliest possible opportunity, at the latest before the next visit. Cases of diagnosed dementia will be adjudicated by the Dementia Adjudication Committee.

Statistical Issues

The results of the study will be analyzed by the Biometry Division of Institut de Recherches Internationales Servier, and validated by the Robertson Centre for Biostatistics, University of Glasgow, UK. We assumed an average annual incidence of 5% for the composite primary endpoint in the aspirin group and an average duration of follow-up of 3 years. For a statistical power of at least 90% in this event-driven trial, we estimate that 18,000 patients are necessary to demonstrate the superiority of terutroban versus aspirin. This corresponds to a relative risk reduction of 13%, using a two-sided test based on exponential survival curves, a 5% type I error rate, and 2,340 expected events. The efficacy analysis will be performed on an intention-to-treat basis. The main comparison of interest is for superiority, though this will be preceded by a noninferiority comparison. The noninferiority comparison will be carried out on the basis of intention to treat with an on-treatment analysis for sensitivity. Time to the primary endpoint will be compared between the groups using a Cox proportional hazards model adjusted for country. The same analyses will be performed for the time to the secondary endpoints.

The safety analysis will involve the description of adverse events and laboratory parameters. Life-threatening, symptomatic intracranial hemorrhages and major bleedings will also be analyzed as time-to-event data. Gastrointestinal hemorrhage and tolerability, and nonvascular death will be reported, as will compliance with study medication, and frequency and reasons for discontinuation of the study drug.

Some subgroups of patients are expected to be clinically relevant, for example, subgroups divided according to age, gender, and presence of cardiovascular risk factors, such as diabetes, history of hypertension, previous myocardial infarction or previous stroke. These subgroups will therefore be the subject of specific analyses. Further subgroup analyses may be prespecified prior to unblinding of treatment allocation if required.

Ancillary Projects

A number of ancillary studies are being carried out in the PERFORM population and will be reported in detail elsewhere. The PERFORM Vascular Project is exploring the vascular properties of terutroban, i.e., carotid intima-media thickness measurements and local arterial stiffness changes assessed by ultrasonography (at baseline and at yearly intervals), while a parallel study is investigating several biomarkers reflecting antiplatelet, antiatherosclerotic, and anti-inflammatory aspects, as well as selected DNA polymorphisms. As stroke is a leading cause of disability, the PERFORM Quality of Life ancillary study is designed to assess the health-related quality of life in treated patients. Finally, the PERFORM MRI ancillary study is planned to evaluate the effects of terutroban on cerebral parameters (i.e., tissue changes related to vascular pathology, brain volume, and brain tissue microstructures).

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Study Organization

Six supervisory committees have been created for the PERFORM Study.

- The Executive Committee (9 members) is responsible for the development of the study protocol and its amendments, in collaboration with the 46 National Coordinators.
- The Steering Committee combines the Executive Committee and the National Coordinators.
- The Critical Events Committee (8 members) independently and blindly adjudicates the endpoints.
- The Dementia Scientific Committee (5 members) oversees the evaluation of cognitive function and dementia within the PERFORM Study.
- The Dementia Adjudication Committee (6 members) is charged with the adjudication of incident cases of dementia.
- An independent Data Monitoring Committee (5 members) is responsible for reviewing accumulating safety and efficacy data on an ongoing basis. It performs interim analyses (group sequential procedure) on the primary endpoint at scheduled time points during the study according to a prespecified plan.

The members of these committees, as well as a list of the investigators for the PERFORM Study, are listed in the Appendix to this paper.

Conclusion

The first patient was randomized in the PERFORM Study in February 2006. Over 19,000 patients have now been recruited, and the baseline characteristics of the population will be published in a separate paper [37]. The Data Monitoring Committee has met seven times since the beginning of the study. No safety concerns have been found, and the committee has recommended continuation of the study at every meeting. The results of the PERFORM Study are expected in 2011.

Appendix

Executive Committee

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Conflict of Interest Statement

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Erratum

In the article by Bousser MG, Amarenco P, Chamorro A et al., entitled "Rationale and design of a randomized, double-blind, parallel-group study of terutroban 30 mg/day versus aspirin 100 mg/day in stroke patients: 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" [Cerebrovasc Dis 2009;27:509–518, DOI: 10.1159/000212671], the name of one of the collaborators listed in the entry "Investigators by Country, Singapore" was erroneously given as N.V. Ramani. The correct name, however, is N. Venketasubramanian.

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