

Terutroban versus aspirin in patients with cerebral ischaemic events (PERFORM): a randomised, double-blind, parallel-group trial



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Summary

Background Patients with ischaemic stroke or transient ischaemic attack (TIA) are at high risk of recurrent stroke or other cardiovascular events. We compared the selective thromboxane-prostaglandin receptor antagonist terutroban with aspirin in the prevention of cerebral and cardiovascular ischaemic events in patients with a recent non-cardioembolic cerebral ischaemic event.

Methods This randomised, double-blind, parallel-group trial was undertaken in 802 centres in 46 countries. Patients who had an ischaemic stroke in the previous 3 months or a TIA in the previous 8 days were randomly allocated with a central interactive response system to 30 mg per day terutroban or 100 mg per day aspirin. Patients and investigators were masked to treatment allocation. The primary efficacy endpoint was a composite of fatal or non-fatal ischaemic stroke, fatal or non-fatal myocardial infarction, or other vascular death (excluding haemorrhagic death). We planned a sequential statistical analysis of non-inferiority (margin 1·05) followed by analysis of superiority. Analysis was by intention to treat. The study was stopped prematurely for futility on the basis of the recommendation of the Data Monitoring Committee. This study is registered, number ISRCTN66157730.

Findings 9562 patients were assigned to terutroban (9556 analysed) and 9558 to aspirin (9544 analysed); mean follow-up was 28·3 months (SD 7·7). The primary endpoint occurred in 1091 (11%) patients receiving terutroban and 1062 (11%) receiving aspirin (hazard ratio [HR] 1·02, 95% CI 0·94–1·12). There was no evidence of a difference between terutroban and aspirin for the secondary or tertiary endpoints. We recorded some increase in minor bleedings with terutroban compared with aspirin (1147 [12%] vs 1045 [11%]; HR 1·11, 95% CI 1·02–1·21), but no significant differences in other safety endpoints.

Interpretation The trial did not meet the predefined criteria for non-inferiority, but showed similar rates of the primary endpoint with terutroban and aspirin, without safety advantages for terutroban. In a worldwide perspective, aspirin remains the gold standard antiplatelet drug for secondary stroke prevention in view of its efficacy, tolerance, and cost.

Funding Servier, France.

Introduction

Stroke is a leading cause of disability, dementia, and death worldwide. Effective measures to prevent cerebrovascular and cardiovascular disease include lowering of blood pressure, statin use, smoking cessation, regular physical exercise, diabetes treatment, carotid surgery or stenting, and antithrombotic drugs such as oral anticoagulants and antiplatelet drugs.¹ Ischaemic stroke accounts for 80–85% of all strokes and more than 70% are non-cardioembolic stroke, mostly due to large artery atheroma or small artery disease of the brain. Antiplatelet drugs are the antithrombotic agents of choice in the secondary prevention of arterial ischaemic events.^{2,3} In the Antithrombotic Trialists' Collaboration meta-analysis, antiplatelet drugs—mostly aspirin—decreased the combined risk of stroke, myocardial infarction, and vascular death by 25%; the risk reduction was 24% after transient ischaemic attack (TIA) or ischaemic stroke.⁴

Aspirin was the first antiplatelet drug used for secondary prevention, and is the most widely used.^{2,3} Findings from double-blind, randomised clinical trials have shown that clopidogrel⁵ and the combination of aspirin and extended-release dipyridamole⁶ were marginally more effective than was aspirin alone in terms of absolute risk reduction of ischaemic stroke, myocardial infarction, and vascular death. A direct comparison of clopidogrel and aspirin plus dipyridamole suggested no difference in this composite endpoint.⁷ The combination of aspirin plus clopidogrel did not significantly reduce vascular risk compared with clopidogrel alone, but did increase the risk of bleedings.⁸ New antiplatelet drugs have emerged to improve the benefit–risk ratio. Cilostazol was non-inferior to aspirin for the secondary prevention of ischaemic stroke in a Japanese trial.⁹ Several other antiplatelet drugs, mostly inhibitors of P2Y₁₂ ADP receptors such as prasugrel, ticagrelor, cangrelor, and elinogrel, have been tested in acute coronary syndromes, but not in long-term prevention.¹⁰

Lancet 2011; 377: 2013–22

Published Online

May 25, 2011

DOI:10.1016/S0140-

6736(11)60600-4

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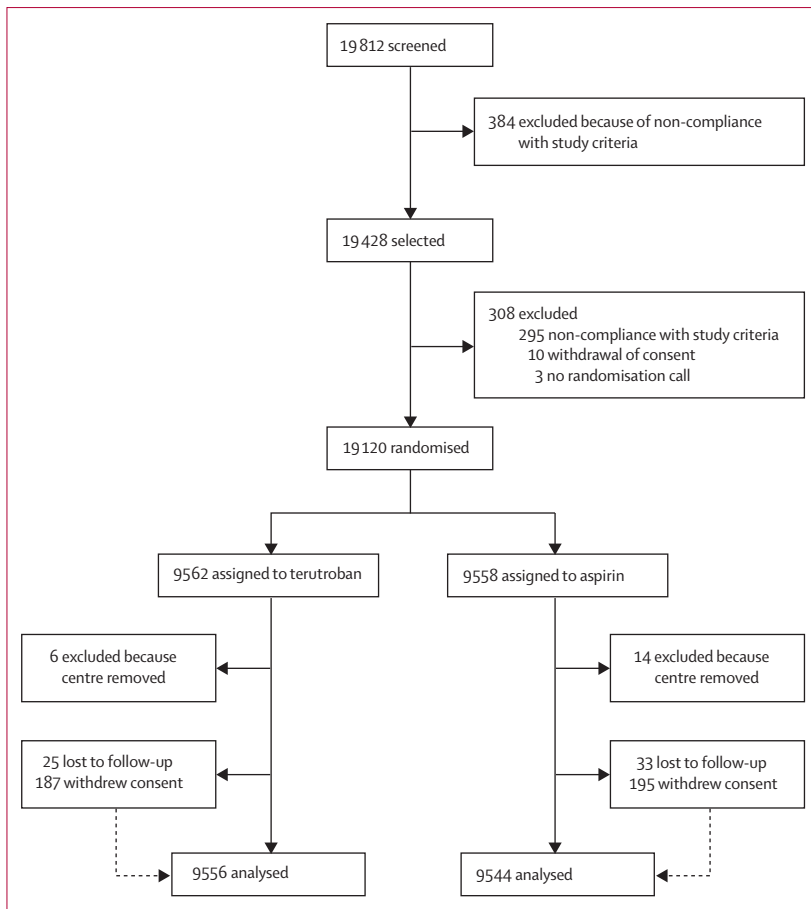


Figure 1: Trial profile

Terutroban, an oral selective antagonist of thromboxane-prostaglandin receptors in platelets and in the vessel wall, was shown in various animal and human studies to be as effective as aspirin in terms of antiplatelet activity.¹¹ Findings from experimental studies also suggested that terutroban had potentially beneficial vascular effects: it improved endothelial function, reduced vascular injury-induced proliferation, and decreased the size of atherosclerotic plaque.¹² On the basis of these results suggesting a beneficial action of terutroban on both thrombus formation and vascular function, together with potential antiatherogenic properties, a large randomised clinical trial of secondary vascular prevention was launched in 2006, to compare terutroban 30 mg per day and aspirin 100 mg per day in patients who had had a cerebral ischaemic event (the Prevention of cerebrovascular and cardiovascular Events of ischaemic origin with teRutroban in patients with a history of ischaemic stroke or transient ischaemic attack [PERFORM] study).

Methods

Study design and participants

PERFORM was an international, multicentre, randomised, double-blind, parallel-group trial. It was designed

to assess the superiority of terutroban compared with aspirin in the prevention of cardiovascular ischaemic events in patients with a recent ischaemic stroke or TIA. The study was undertaken in 802 centres in 46 countries. Patients were randomly assigned between Feb 22, 2006, and April 7, 2008. The study design has been published elsewhere.¹³ Briefly, eligible patients were men or women, aged 55 years or older, who had had an ischaemic stroke or arterial retinal ischaemic event more than 48 h and less than 3 months preceding inclusion, or a TIA in the previous 8 days. Ischaemic stroke was defined as a focal ischaemic neurological deficit lasting at least 24 h, or lasting less than 24 h but confirmed by brain imaging. TIA was a focal deficit including at least motor weakness in the limbs or aphasia and lasting less than 24 h in the absence of imaging evidence of corresponding cerebral infarction. Ischaemic stroke subtypes were categorised into six groups: atherothrombotic, likely atherothrombotic, lacunar, cardioembolic, coexisting (atherothrombotic and lacunar), or unknown according to a previously described classification.^{13,14} Major exclusion criteria were cognitive impairment or known dementia, and cardiac sources of embolism requiring long-term oral anticoagulation.

The study conformed to the ethical principles set out in the Declaration of Helsinki and was approved by independent ethics committees in all countries. All patients provided written informed consent before study entry.

Randomisation and masking

Patients were randomly allocated to receive 30 mg per day terutroban (Les Laboratoires Servier Industries, Gidy, France) or 100 mg per day aspirin (enteric-coated tablet; Bayer, Leverkusen, Germany) in the morning, starting the day after randomisation, with use of a central interactive response system (telephone or internet). The allocation sequence was generated by the sponsor through in-house application software. The randomisation was balanced, non-adaptive, and stratified by country, with blocks of size four. To enrol and assign the patient to the treatment group, the investigator had to contact a central interactive response system. Patients and investigators were masked to treatment allocation, and the study treatments (terutroban and aspirin) had identical appearance. Investigators were advised to follow guidelines for vascular risk factor management,¹ but not to use aspirin. Study visits took place at 1, 3, and 6 months, and then every 6 months until the closure of the study.

Procedures

The primary endpoint was a composite of fatal or non-fatal ischaemic stroke, fatal or non-fatal myocardial infarction, or other vascular death (excluding haemorrhagic death). Secondary endpoints were: a composite of any stroke, any myocardial infarction, or other vascular death (excluding haemorrhagic death); each component

of the primary endpoint separately; all-cause mortality; any stroke; fatal stroke; any ischaemic stroke; any myocardial infarction; cognitive decline; and dementia. Tertiary endpoints were: admission to hospital or prolongation of hospital stay for cardiac reasons; cardiac death; revascularisation; carotid revascularisation; major lower-limb amputation; disabling or fatal stroke; number of patients with more than one stroke; and disability (defined by a Barthel Index <95 at the last visit).

Safety assessment included reported adverse events, notably haemorrhagic events (intracranial haemorrhage, gastrointestinal bleeding and all other bleedings) and gastrointestinal tolerability, and laboratory parameters and vital signs (blood pressure and heart rate). Bleeding was adjudicated and classified by the Critical Events Committee as life-threatening (defined by a fatal outcome, a reduction in haemoglobin of 50 g/L or more, symptomatic intracranial haemorrhage, or transfusion of 4 units or more of red blood cells); major (defined by a significantly disabling bleeding, an intraocular bleeding leading to significant loss of vision, a transfusion of 3 units or less of red blood cells, or needing hospital admission or surgery); or minor (defined by any other bleedings).

Statistical analysis

This event-driven trial was designed to test the superiority of terutroban versus aspirin, preceded by a non-inferiority analysis, with a non-inferiority margin for the hazard ratio (HR) of terutroban relative to aspirin of 1.05. With the assumption of an HR of 0.87 with 90% power and 5% significance level, 2340 primary endpoints were needed, resulting in 18000 patients to be randomly assigned with a 5% yearly event rate for the primary outcome in the aspirin group and an average follow-up of 3 years.

The independent Data Monitoring Committee undertook two interim efficacy analyses: one to detect premature efficacy and one to investigate both premature efficacy and futility. The type I error rate was fixed at 0.01% for the first interim efficacy analysis and at 0.1% for the second. Futility was considered if the observed estimate for HR was more than 1 and the 95% CI was greater than 0.93.

Baseline characteristics were summarised as numbers of patients (%) for categorical variables and means (SD) for continuous variables. Efficacy outcomes were adjudicated and analysed with the intention-to-treat principle. Time-to-first-event outcomes were analysed with Cox's proportional hazards model with adjustment for country to estimate the treatment effect and the associated 95% CI. Time-to-event curves were estimated by the Kaplan-Meier method. Similar analyses were done for the primary endpoint in predefined baseline subgroups (age ≥ 75 vs <75 years, sex, history of diabetes, stroke subtype, history of ischaemic stroke, history of coronary artery disease, history of hypertension, use of statins, and use of

angiotensin-converting enzyme [ACE] inhibitor), with treatment by subgroup interaction investigated within the Cox models. For incident dementia and cognitive decline, the odds ratio for terutroban relative to aspirin was estimated with a logistic regression model. Safety analyses were done on events occurring on treatment. Emergent adverse events, selected adverse events, and adverse

	Terutroban group (n=9556)	Aspirin group (n=9544)
Demographic characteristics		
Men	6031 (63%)	5919 (62%)
Age (years)	67.2 (7.9)	67.3 (7.9)
<65	3933 (41%)	3903 (41%)
≥ 65 –<75	3707 (39%)	3718 (39%)
≥ 75	1916 (20%)	1923 (20%)
Ethnic origin		
White	7995 (84%)	8031 (84%)
Asian	1122 (12%)	1122 (12%)
Black	172 (2%)	147 (2%)
Other	267 (3%)	244 (3%)
Physical examination		
BMI (kg/m ²)	27.1 (4.3)	27.1 (4.3)
SBP (mm Hg)	138.5 (17.0)	138.0 (16.6)
DBP (mm Hg)	80.2 (9.5)	80.0 (9.4)
Heart rate (beats per min)	71.6 (10.5)	71.6 (10.4)
Smoking habits		
Never smoked	4622 (48%)	4690 (49%)
Current smoker	2559 (27%)	2515 (26%)
Stopped smoking >6 months previously	2373 (25%)	2338 (25%)
Medical history		
Hypertension	8011 (84%)	7953 (83%)
Hypercholesterolaemia	4596 (48%)	4587 (48%)
Hypertriglyceridaemia	906 (9%)	892 (9%)
Diabetes	2692 (28%)	2607 (27%)
Previous ischaemic stroke	1444 (15%)	1449 (15%)
Previous TIA	697 (7%)	741 (8%)
Angina pectoris	886 (9%)	927 (10%)
Myocardial infarction	736 (8%)	739 (8%)
Peripheral artery disease	378 (4%)	361 (4%)
Previous treatments*		
Antiplatelet drugs	8890 (93%)	8852 (93%)
Aspirin	8286 (87%)	8202 (86%)
Dipyridamole	906 (9%)	911 (10%)
Clopidogrel	702 (7%)	753 (8%)
Aspirin and dipyridamole combined	482 (5%)	498 (5%)
Ticlopidine	112 (1%)	129 (1%)
Statin	5534 (58%)	5519 (58%)
ACE inhibitor	5267 (55%)	5164 (54%)
ARB	1323 (14%)	1337 (14%)
Diuretic	3468 (36%)	3391 (36%)
Calcium-channel blocker	2664 (28%)	2643 (28%)
β blocker	2561 (27%)	2624 (27%)
Antidiabetic agent	2199 (23%)	2105 (22%)

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	Terutroban group (n=9556)	Aspirin group (n=9544)
(Continued from previous page)		
Qualifying event and stroke characteristics		
Qualifying event		
Ischaemic stroke	8574 (90%)	8527 (89%)
ARIE	38 (<1%)	32 (<1%)
TIA	942 (10%)	982 (10%)
Unknown	2 (<1%)	3 (<1%)
Ischaemic stroke subtype		
Atherothrombotic stroke†	877 (10%)	936 (11%)
Likely atherothrombotic stroke †	3532 (41%)	3569 (42%)
Lacunar stroke†	856 (10%)	877 (10%)
Cardioembolic stroke†	80 (1%)	89 (1%)
Rare causes	0	7 (<1%)
Coexisting	1327 (15%)	1231 (14%)
Unknown cause	1902 (22%)	1818 (21%)
Delay between ischaemic stroke and randomisation‡ (days)		
≤1 week	1612 (19%)	1672 (19%)
>1 week to ≤1 month	4304 (50%)	4160 (49%)
>1 month	2687 (31%)	2715 (32%)
Delay between TIA and randomisation (days)		
	5.6 (5.1)	5.9 (5.5)
Modified Rankin scale		
Class 0 (no symptoms)	2114 (22%)	2123 (22%)
Class 1 (no significant disability)	3669 (38%)	3647 (38%)
Class 2 (slight disability)	2135 (22%)	2160 (23%)
Class 3 (moderate disability)	1059 (11%)	987 (10%)
Class 4 (moderately severe disability)	578 (6%)	620 (6%)
Mini-mental state examination score		
<15	81 (1%)	84 (1%)
15-23	849 (9%)	818 (9%)
>23	8532 (90%)	8547 (90%)
Data are number of patients (%) or mean (SD). BMI=body-mass index. SBP=systolic blood pressure. DBP=diastolic blood pressure. TIA=transient ischaemic attack. ACE=angiotensin-converting enzyme. ARB=angiotensin II receptor blocker. ARIE=arterial retinal ischaemic event. *Treatment between qualifying event and randomisation. †Subtype without coexisting cause. ‡Including ARIE.		

Table 1: Baseline characteristics

events leading to study drug withdrawal were tabulated by treatment group.

On Oct 12, 2009, the Data Monitoring Committee recommended that the PERFORM trial be stopped because the study was most unlikely to show any benefit of the study drug compared with aspirin. This recommendation was ratified by the Executive Committee on Oct 23, 2009; between November, 2009, and March, 2010, the investigators recalled patients for the final end-of-study visit.

PERFORM is registered, number ISRCTN66157730.

Role of the funding source

The PERFORM Executive Committee designed the study, interpreted the results, wrote the report, and had full access to all study data. The sponsor of the study was responsible for data management and final data analyses.

All analyses were verified by the independent statistical centre at Robertson Centre for Biostatistics, University of Glasgow, UK. The sponsor supported the work of the Executive Committee, but did not make any scientific or research decisions independent of this Committee. All members of the Executive Committee had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the trial profile. 19120 patients were randomly allocated to treatment (9562 to terutroban, 9558 to aspirin). During follow-up, one centre, which had included 20 randomised patients, was removed from the trial before unmasking because of invalid data caused by misconduct. Therefore, the efficacy analysis included 19100 patients (9556 terutroban, 9544 aspirin).

The mean duration of follow-up was 28.3 months (SD 7.7). The clinical status of all patients was ascertained at study closure, apart from 58 (<1%) patients lost to follow-up and 382 (2%) who withdrew consent (figure 1). These patients were censored at their last contact time.

Baseline characteristics of the study population were similar in both treatment groups (table 1). The mean age of the population was 67.2 years (SD 7.9). 11950 (63%) were men, and 16026 (84%) were white. The most frequent risk factors were hypertension, hypercholesterolaemia, past history of smoking or current smoking, and diabetes (table 1). Nearly a quarter of the population had an ischaemic stroke or TIA before the qualifying event (table 1). Most patients received antiplatelet drugs between the qualifying event and randomisation (table 1).

Qualifying events were ischaemic stroke, TIA, or arterial retinal ischaemic event (table 1). Ischaemic strokes, categorised according to a predefined classification,¹³ were atherothrombotic or likely atherothrombotic in 8914 (52%) patients, lacunar in 1733 (10%), and coexisting in 2558 (15%). When combining pure and coexisting subtypes, 11447 (67%) ischaemic strokes were atherothrombotic or likely atherothrombotic and 3940 (23%) lacunar. The mean delay between qualifying event and randomisation was 26.9 days (SD 23.9) for ischaemic stroke or arterial retinal ischaemic event, and 5.8 days (5.3) for TIA. The population had no or slight disability, with a modified Rankin scale score of 2 or less in 15848 (83%) patients. Mini-mental state examination score was greater than 23 in 17079 (90%) patients. Premature discontinuation of study drug occurred in 4244 (22%) patients and was similar in the two groups (data not shown).

There were 2153 primary composite endpoints during the course of the study (table 2), which was 92% of the planned target number. Of these events, there were 1533 fatal or non-fatal ischaemic strokes (777 in the terutroban group vs 756 in the aspirin group), 263 fatal or non-fatal myocardial infarctions (145 vs 118), and 357 other

vascular deaths (169 vs 188). The primary composite event occurred in 1091 (11%) patients receiving terutroban versus 1062 patients (11%) receiving aspirin (HR 1.02, 95% CI 0.94–1.12; figure 2, table 2), which did not meet the non-inferiority criterion.

We recorded no significant difference in efficacy for any of the other secondary and tertiary endpoints explored in the trial (table 2). Notably, the rate of any ischaemic stroke was 8% in both groups (table 2). Similarly, we noted no significant differences between groups in myocardial infarction or vascular death (table 2).

Analysis of efficacy for the primary composite endpoint in prespecified subgroups showed no difference related to age, sex, qualifying event, history of diabetes, coronary artery disease, hypertension, or use of statins or ACE inhibitors at baseline (figure 3). However, we noted a difference in the magnitude of treatment effect ($p=0.003$ for interaction) in patients with a history of ischaemic stroke before the qualifying event, with a lower event rate with terutroban than with aspirin (figure 3).

Safety was assessed in all patients with at least one exposure to study treatment (9479 terutroban, 9466 aspirin). The occurrence of adverse events was similar in the two groups, with 7947 (84%) of the terutroban group reporting at least one adverse event versus 7940 (84%) of the aspirin group. Of these events, 2975 (31%) were regarded as serious and 911 (10%) led to treatment withdrawal in the terutroban group, versus 3126 (33%) and 901 (10%) in the aspirin group, respectively. The main adverse events included inadequately controlled blood pressure (1569 [17%] in terutroban group vs 1580 [17%] in aspirin group), hypercholesterolaemia (738 [8%] vs 692 [7%]), and depression (631 [7%] vs 707 [8%]). Bleedings occurred significantly more with terutroban than with aspirin because of an increase in occurrence of minor bleedings (table 3). We recorded no significant difference in major or life-threatening bleedings (table 3). Intracranial haemorrhage occurred in less than 2% of the population, with no difference between groups (table 3). We noted no difference in the occurrence of gastrointestinal bleedings or intolerance (table 3). Furthermore, we recorded no differences between groups in mean blood pressure, heart rate, or laboratory parameters throughout the study (data not shown).

Discussion

The PERFORM trial did not show superiority of terutroban compared with aspirin in the prevention of non-haemorrhagic cardiovascular events. PERFORM was designed to show superiority of terutroban with the assumption of a 13% relative risk reduction with at least 90% power. Even though the rate of primary endpoints in each treatment group reached 11%, it did not meet the stringent non-inferiority criterion, corresponding to a margin of 1.05. Furthermore, we recorded no significant difference between the two

	Terutroban (n=9556)	Aspirin (n=9544)	HR* (95% CI)
Primary composite endpoint			
Fatal or non-fatal ischaemic stroke, fatal or non-fatal MI, and other vascular death†	1091 (11%)	1062 (11%)	1.02 (0.94–1.12)
Secondary endpoints			
Secondary composite endpoint			
Any stroke (fatal or non-fatal), fatal or non-fatal MI, and other vascular death†	1151 (12%)	1122 (12%)	1.02 (0.94–1.11)
Stroke-related endpoints			
Fatal or non-fatal ischaemic stroke	781 (8%)	763 (8%)	1.02 (0.92–1.13)
Non-fatal ischaemic stroke	728 (8%)	724 (8%)	1.00 (0.90–1.11)
Fatal ischaemic stroke	64 (1%)	49 (1%)	1.30 (0.90–1.89)
Any stroke	842 (9%)	828 (9%)	1.01 (0.92–1.12)
Any fatal stroke	98 (1%)	78 (1%)	1.25 (0.93–1.69)
Number of patients with more than one stroke	104 (1%)	93 (1%)	..
MI-related endpoints			
Fatal or non-fatal MI	159 (2%)	129 (1%)	1.23 (0.98–1.56)
Non-fatal MI	140 (1%)	114 (1%)	1.23 (0.96–1.58)
Fatal MI	26 (<1%)	21 (<1%)	1.24 (0.70–2.20)
Mortality-related endpoints			
Other vascular death†	215 (2%)	224 (2%)	0.95 (0.79–1.15)
All-cause mortality	594 (6%)	587 (6%)	1.01 (0.90–1.13)
Cognition-related endpoints			
Incident dementia‡	162 (2%)	155 (2%)	1.05 (0.84–1.31)
Cognitive decline§	3301 (38%)	3392 (39%)	0.96 (0.90–1.02)
Tertiary endpoints			
Hospitalisation due to cardiac causes	464 (5%)	435 (5%)	1.07 (0.94–1.22)
Cardiac death	52 (1%)	54 (1%)	0.96 (0.66–1.41)
Disabling or fatal stroke	688 (7%)	698 (7%)	0.98 (0.88–1.09)
Revascularisation	313 (3%)	324 (3%)	0.97 (0.83–1.13)
Carotid revascularisation	22 (<1%)	26 (<1%)	0.84 (0.48–1.49)
Major lower limb amputation	33 (<1%)	21 (<1%)	1.57 (0.91–2.71)
Data are number of first events (%) and HR (95% CI). HR=hazard ratio. MI=myocardial infarction. *Odds ratio for cognition-related endpoints. †Vascular death excludes haemorrhagic death of any origin. ‡Number of patients without dementia at baseline: 9424 terutroban, 9428 aspirin. §Number of patients without dementia at baseline and with available scores: 8761 terutroban, 8762 aspirin.			

Table 2: Efficacy for primary, secondary, and tertiary endpoints

treatment groups for the 14 secondary and the six tertiary predefined endpoints.

The frequency of the primary composite endpoint in the prespecified subgroups according to age, sex, type of qualifying event, and history of diabetes or hypertension was similar in the two groups. The only significant treatment effect interaction between groups was in relation to patients with a history of ischaemic stroke before the qualifying event, who had a lower event rate with terutroban. Although this finding could be attributable to chance, it is plausible since most of these patients would have been receiving aspirin before their PERFORM qualifying event and would therefore have had a further ischaemic event despite aspirin. A different antiplatelet drug might therefore be expected to be more effective than continuation of aspirin.

Minor bleedings occurred significantly more frequently with terutroban than with aspirin, although we noted no difference in major or life-threatening bleedings or in intracranial haemorrhage between

groups. We did not record an expected benefit of terutroban compared with aspirin in terms of gastrointestinal bleedings and intolerance. The slight excess in minor bleedings with terutroban 30 mg per day suggests that higher doses would have been detrimental in PERFORM, given that the bleeding risk seems to depend on the number of thromboxane-prostaglandin receptors bound by the drug.

PERFORM was designed as a superiority trial because previous experimental and human studies had suggested that terutroban had an antiplatelet activity at least as strong as that of aspirin, together with potentially beneficial vascular effects not documented for aspirin. Terutroban was at least as effective as aspirin in inhibition of platelet aggregation induced by arachidonic acid, collagen, and antiplatelet drugs in patients with peripheral arterial disease,¹⁵ and was superior to aspirin in inhibition of platelet aggregation and thrombus formation in an ex-vivo model of thrombosis in a pilot study of patients at risk of ischaemic stroke.¹⁶ Theoretically, there are two main mechanisms by which terutroban might have been a more potent antithrombotic agent than aspirin: terutroban does not suppress the cardioprotective eicosanoid prostacyclin; and it blocks thromboxane-prostaglandin receptor activation by unconventional ligands such as isoprostanes. However,

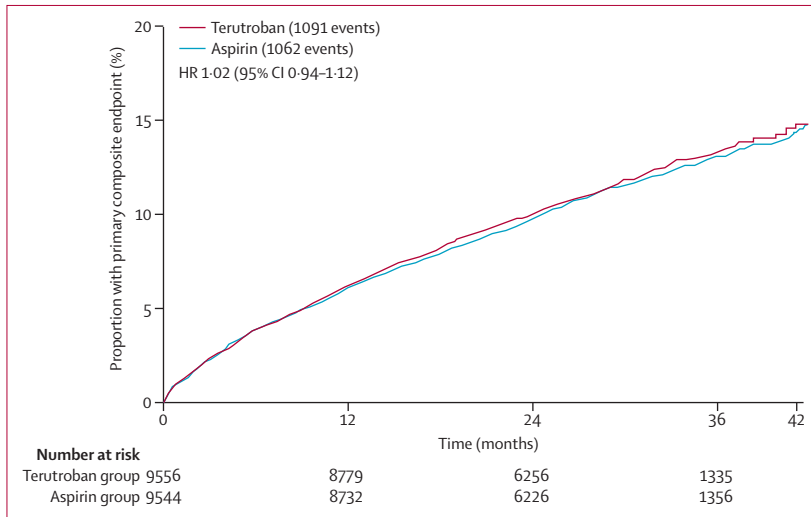


Figure 2: Kaplan-Meier cumulative event curves for the primary composite endpoint of fatal or non-fatal ischaemic stroke, fatal or non-fatal myocardial infarction, and other vascular death (excluding haemorrhagic death) HR=hazard ratio.

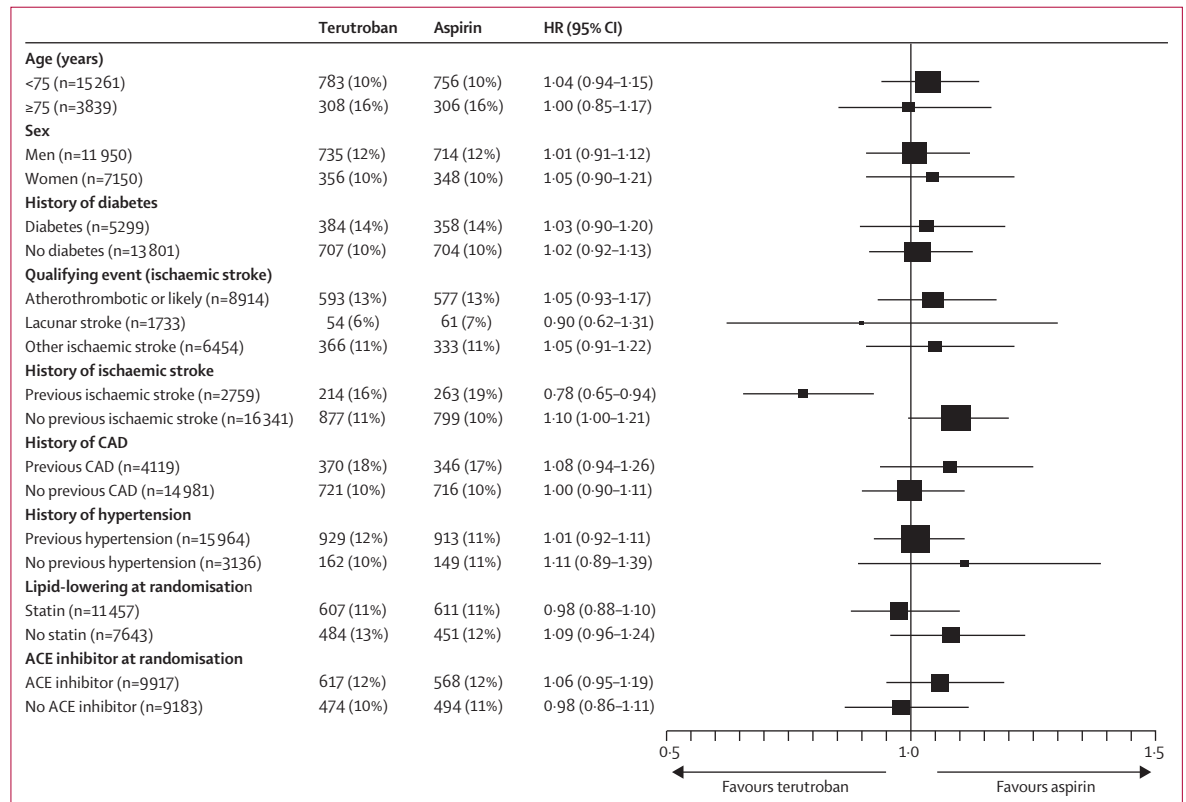


Figure 3: Efficacy for primary composite endpoint of fatal or non-fatal ischaemic stroke, fatal or non-fatal myocardial infarction, and other vascular death (excluding haemorrhagic death) according to prespecified subgroups Data are number (%) of patients with first events. HR=hazard ratio. CAD=coronary artery disease. ACE=angiotensin-converting enzyme.

the failure to detect a benefit of terutroban compared with aspirin in PERFORM suggests that the clinical consequences of inhibition of thromboxane A₂-induced platelet aggregation by a thromboxane-prostaglandin receptor antagonist do not differ from those obtained by suppression of thromboxane A₂ formation by platelet COX1 inhibition with aspirin. This apparent discrepancy draws attention to the limitations of ex-vivo measurements of platelet function in prediction of platelet activation and inhibition in vivo.¹⁷

In addition to its antithrombotic effect, terutroban has antivasoconstrictive effects and improves blood flow by selectively increasing endothelium-dependent vasodilation.¹⁸ Although endothelium-dependent contractions are increased by vascular risk factors¹⁹ such as age, hypertension, and diabetes, which were highly prevalent in PERFORM, we detected no benefit, which might suggest that there is no direct relation between endothelium-dependent contractions and the risk of ischaemic stroke. The antiproliferative effect of terutroban, as shown in a model of vascular injury-induced proliferation in the mouse carotid artery,²⁰ did not translate into a clinical benefit, in line with the inability of previously developed thromboxane-prostaglandin receptor antagonists to prevent postcoronary angioplasty restenosis.²¹⁻²³ Terutroban has well documented antiatherogenic properties, which led to the preferential recruitment of patients with an atherothrombotic cerebral ischaemic event in this study. Indeed, the size of aortic plaques was significantly smaller in apoE-deficient mice fed a fat-rich diet receiving terutroban than in those receiving aspirin.²⁴ Similarly, mice fed a high-fat diet had significantly fewer aortic atherosclerotic lesions when terutroban was added to their drinking water.²⁵ In PERFORM, we recorded no benefit for terutroban compared with aspirin, even in the subgroup of patients with an atherothrombotic ischaemic stroke at entry, possibly because their atheromatous lesions were already well advanced.

We do not think that the trial design, performance, or analysis are likely to have resulted in any significant biases in estimation of the treatment effect. The trial had centralised balanced randomisation with stratification by country, and all outcome events were subject to central blind adjudication. The trial was double blind with identical study drug and placebo, there were no major differences between the treatment groups in side-effects that might have resulted in loss of masking, and rates of premature discontinuation of study drug were similar in the two groups. The analysis plan (including all nine subgroups) was prespecified and the primary analysis was by intention to treat.

However, our trial does have some limitations. First, we had too few patients randomised acutely after TIA or stroke to detect reliably any difference in treatment effect on very early recurrent stroke. Second, given that only 15% of patients were followed up to or beyond 3 years, we cannot be certain that a difference in treatment effect

	Terutroban (n=9479)	Aspirin (n=9466)	HR (95% CI)
Bleedings			
All bleedings	1462 (15%)	1360 (14%)	1.09 (1.01-1.17)
Life-threatening bleedings	199 (2%)	206 (2%)	0.96 (0.79-1.16)
Major bleedings	211 (2%)	210 (2%)	1.01 (0.83-1.22)
Minor bleedings	1147 (12%)	1045 (11%)	1.11 (1.02-1.21)
Intracranial haemorrhage			
All intracranial haemorrhage	146 (2%)	121 (1%)	1.20 (0.94-1.53)
Fatal intracranial haemorrhage	36 (<1%)	28 (<1%)	1.28 (0.78-2.09)
Parenchymal haemorrhage	67 (1%)	58 (1%)	1.14 (0.80-1.62)
Stroke of unknown type	42 (<1%)	24 (<1%)	1.74 (1.05-2.88)
Other*	45 (<1%)	44 (<1%)	1.02 (0.67-1.55)
Gastrointestinal disorders			
Gastrointestinal bleedings	305 (3%)	316 (3%)	0.97 (0.83-1.13)
Gastrointestinal intolerance	1227 (13%)	1294 (14%)	0.94 (0.87-1.02)

Data are number of first events (%) and HR (95% CI). HR=hazard ratio. *Subdural haematoma, haemorrhagic transformation, subarachnoid haemorrhage, and epidural haematoma.

Table 3: Frequency of selected adverse events

Panel: Research in context

Systematic review

We searched PubMed and Medline for articles on stroke prevention published in English up to December, 2010, with the terms "aspirin", "secondary prevention of stroke", "antiplatelet agents", "S18886", "terutroban", and "TXA₂ receptor blockade". We also undertook separate subsearches with a cross-search of the above terms combined, and the reference lists of the selected articles. We selected studies considered to be relevant to the discussion, and identified PROFESS⁷ as the largest study ever undertaken for secondary prevention of stroke.

Interpretation

The PERFORM study, the second largest secondary prevention antiplatelet drug trial undertaken in patients with a recent cerebral ischaemic event, did not show a clinical benefit of terutroban compared with aspirin. This finding was unexpected in view of evidence that terutroban has antiplatelet and antithrombotic effects at least as strong as aspirin in patients with peripheral arterial disease or ischaemic stroke,^{15,16} and vascular effects not shown with aspirin. Moreover, it was significantly superior to placebo on endothelial dysfunction assessed by the forearm hyperaemia test in atheromatous patients.¹⁸ In animals, terutroban showed antivasoconstrictive, antiproliferative, anti-inflammatory, and antiatherogenic effects.^{11,24,25} After the premature discontinuation of PERFORM, the sponsor decided to stop the development of terutroban, including all other terutroban trials in progress. However, the PERFORM results lend themselves to speculation about specific clinical settings in which blockade of the thromboxane-prostaglandin receptor might confer advantage compared with low-dose aspirin such as: reperfusion situations in which there is an increase in isoprostane generation leading to thromboxane-prostaglandin activation; some varieties of small artery diseases of the brain, in which there is a failure of small arteries to dilate properly; early restenosis after carotid endarterectomy or stenting; and early atheroma in young patients at high vascular risk.

might not have emerged late, perhaps related to the additional potential longer-term effects of terutroban. Third, we did not prespecify the expected direction of subgroup-treatment effect interactions, which makes interpretation of the observed difference in effect in

relation to previous history of ischaemic stroke more difficult. Finally, the results might not be valid for patients younger than 55 years who have had a stroke due to cardiac embolism or who are clinically unstable, because none of these patients were enrolled in this trial.

PERFORM is the second largest secondary prevention trial of an antiplatelet drug undertaken so far in patients with cerebral ischaemic events (panel). The largest study, PROFESS,⁷ compared aspirin plus extended-release dipyridamole and clopidogrel in 20 232 patients followed up for a mean of 30 months. The main baseline characteristics of patients recruited in the two studies were very similar in terms of age, sex, and frequency of major vascular risk factors, and were broadly representative of patients with a non-cardioembolic cerebral ischaemic event. However, there was a difference in patients' ethnic origin between the two trials: 58% (11 697) patients were white or European in PROFESS versus 84% (16 026) in PERFORM. The type and presumed cause of the qualifying events also differed, with the inclusion of TIAs in PERFORM but not in PROFESS. Furthermore, the proportion of atherothrombotic and lacunar infarcts differed in the two studies: 67% (11 447) and 23% (3940) in PERFORM versus 28% (5805) and 52% (10 578) in PROFESS, respectively. Despite these differences, the event rates were remarkably close in the two studies, allowing estimation of the yearly risk of recurrent ischaemic stroke at 3.5% and the composite endpoint of stroke, myocardial infarction, and vascular death at 4.5% in patients with a recent non-cardioembolic cerebral ischaemic event.

In conclusion, PERFORM did not show non-inferiority of terutroban compared with aspirin in the prevention of cardiovascular ischaemic events in patients with a non-cardioembolic cerebral ischaemic event. We detected no safety advantage for terutroban. In view of these results, whether there are other specific clinical settings in which selective thromboxane-prostaglandin receptor blockade might confer an advantage over low-dose aspirin remains unknown.

Contributors

All authors participated in the design of the study, the interpretation of the data, and the writing of the Article. The statistical analysis was done by the sponsor, and was verified by the independent trial statistical centre in the Robertson Centre for Biostatistics (Michele Robertson), University of Glasgow, UK. All authors have read and approved the final version.

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Conflicts of interest

MGB has received travel and accommodation support for meetings from Servier and Sanofi-Aventis, and research funding and grants from Servier, Sanofi-Aventis, Fondation Bouygues, INSERM, and Ministère du travail, de l'emploi et de la santé. PA has received honoraria for talks, advisory boards, or clinical trial committees from Pfizer, Astra-Zeneca, Bayer, Boehringer Ingelheim, Sanofi-Aventis, Bristol-Myers Squibb, Lundbeck, PAION, Novartis, Merck, EV3, and Servier; and has received research funding from Pfizer, Sanofi-Aventis, Servier and Boehringer Ingelheim. AC has received honoraria for talks, advisory boards, and clinical trial committees from Boehringer Ingelheim, Grupo Ferrer, Sanofi-Aventis, Bristol-Myers Squibb, Pfizer, Servier, and Sygnis Bioscience; and has received research funding from Boehringer Ingelheim. MF has received consulting fees, travel fees, and research grants from Servier. IF has received research grants, support for attending conferences, and study Executive Committee honoraria from Servier. KMF has received fees, honoraria, and research grants from Servier. MGH has received honoraria for talks, travel support, and advisory board membership from Servier; additionally, he also received similar support from Boehringer Ingelheim, Sanofi-Aventis, Bristol-Myers Squibb, Bayer, Novartis, and Pfizer. HPM has received honoraria for lectures, advisory boards, and clinical trial committees from Bayer, Biogen, Boehringer Ingelheim, Merck, Novartis, Pfizer, Servier, and Teva; and research support from

Bayer, Biogen, and Pfizer. PMR has received honoraria for talks, advisory boards, and clinical trial committees from Astra-Zeneca, Bayer, Boehringer Ingelheim, Sanofi-Aventis, Bristol-Myers Squibb, and Servier; and has received research funding from Boehringer Ingelheim. AdC and MDF are employed by Servier.

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