Thromboxane Prostaglandin Receptor Antagonist and Carotid Atherosclerosis Progression in Patients With Cerebrovascular Disease of Ischemic Origin
A Randomized Controlled Trial

Michiel L. Bots, MD, PhD; Ian Ford, PhD; Suzanne M. Lloyd, MSc; Stephane Laurent, MD, PhD; Pierre J. Touboul, MD, PhD; Michael G. Hennerici, MD, PhD; on behalf 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 Vascular Ultrasound Study Investigators

Background and Purpose—Thromboxane prostaglandin receptors have been implicated to be involved in the atherosclerotic process. We assessed whether Terutroban, a thromboxane prostaglandin receptor antagonist, affects the progression of atherosclerosis, as measured by common carotid intima-media thickness and carotid plaques.

Methods—A substudy was performed among 1141 participants of the aspirin-controlled Prevention of Cerebrovascular and Cardiovascular Events of Ischemic Origin with Terutroban in Patients with a History of Ischemic Stroke or Transient Ischemic Attack (PERFORM) trial. Common carotid intima-media thickness and carotid plaque occurrence was measured during a 3-year period.

Results—Baseline characteristics did not differ between Terutroban (n=592) and aspirin (n=549) treated patients and were similar as in the main study. Mean study and treatment duration were similar (28 and 25 months, respectively). In the Terutroban group, the annualized rate of change in common carotid intima-media thickness was 0.006 mm per year (95% confidence interval, –0.004 to 0.016) and –0.005 mm per year (95% confidence interval, –0.015 to 0.005) in the aspirin group. There was no statistically significant difference between the groups in the annualized rate of change of common carotid intima-media thickness (0.011 mm per year; 95% confidence interval, –0.003 to 0.025). At 12 months of follow-up, 66% of Terutroban patients had no emergent plaques, 31% had 1 to 2 emergent plaques, and 3% had ≥3 emergent plaques. In the aspirin group, the corresponding percentages were 64%, 32%, and 4%. Over time, there was no statistically significant difference in the number of emergent carotid plaques between treatment modalities (rate ratio, 0.91; 95% confidence interval, 0.77–1.07).

Conclusions—Compared with aspirin, Terutroban did not beneficially affect progression of carotid atherosclerosis among well-treated patients with a history of ischemic stroke or transient ischemic attacks with an internal carotid stenosis <70%.


Key Words: atherosclerosis ■ carotid intima-media thickness ■ randomized controlled trial

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large number of randomized trials to assess the effect of an intervention on atherosclerosis progression. Similarly, change in plaque occurrence over time has been shown to be a suitable outcome measurement in trials.

We, therefore, set out to assess the antiatherosclerotic properties of Terutroban in a dedicated vascular study, nested 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) trial.

The PERFORM trial was undertaken in 802 centers in 46 countries and included 9562 patients assigned to 30 mg per day Terutroban and 9558 assigned to 100 mg per day aspirin with a history of ischemic stroke or transient ischemic attack. The study was stopped prematurely after a negative futility analysis. Although the study did not meet the predefined criteria for noninferiority, the results showed that Terutroban and aspirin had similar effects of the primary combined end point (fatal or nonfatal ischemic stroke, myocardial infarction, or vascular death). No significant differences for safety were reported. We report here the results of the PERFORM Vascular Ultrasound Project.

Methods

The design of this ancillary study is presented briefly because a detailed protocol has been reported elsewhere. The PERFORM Vascular Ultrasound Project was performed in 56 centers in 16 countries. The first patient was recruited in February 2006, and the last patient was randomized in March 2008. The study protocol was approved by the local ethic committees, and all patients gave written informed consent. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Inclusion Criteria

Patients were men and women aged 55 to 80 years participating in PERFORM. They had a history of cerebral or retinal infarction within the past 3 months or a transient ischemic attack within the past 8 days and were stable at inclusion (no intracranial hemorrhage or nonischemic neurological disease). For inclusion in the ancillary study, they should have had a baseline vascular evaluation of the carotid arteries. Eligibility was based on a quality assessment of the images confirming that both common carotid arteries (CCAs) were visible and that the start of the reading process. In addition, reproducibility studies were performed before and during central batch reading to determine whether reproducibility was satisfactory throughout the study. A technical evaluation of ultrasound equipment using a phantom was performed before and during central batch reading to determine whether reproducibility was satisfactory throughout the study.

Carotid Ultrasound Imaging

Common CIMT and plaque assessments were obtained with a high-resolution B-mode duplex ultrasound scanner (linear array ≥7 MHz, or broadband 5 to ≥10 MHz). Ultrasound data collection and analysis were performed according to Mannheim Consensus recommendations. All images were transferred to a centralized imaging laboratory (Bioclinica, Leiden, the Netherlands). Images were sent in a standard Digital Imaging and Communications in Medicine format. Image acquisition parameters were harmonized (depth =±4 cm), single focus zone, no zoom, high frame rate, low persistence, and optimized gain settings) to ensure optimal image quality, which was verified after every vascular examination along with protocol compliance and data completeness. At baseline, the CCA region of interest was visualized at an angle showing the clearest boundaries of the near and far wall. The CCA region of interest was also visualized at 3 prespecified angles that differed from one another by 30° using the Meijer carotid arc. The optimal angle for visualizing CCA near and far wall boundaries was noted at baseline and used as a reference in the follow-up and for analysis.

The CCA segment ≤10 mm proximal to the bifurcation was defined as the region of interest for common CIMT measurement. Common CIMT measurements were taken from a longitudinal view of a 10-mm plaque-free segment of the far wall of the right and left CCAs. Longitudinal and transverse images of the right and left carotid trees (CCA, bifurcation, and internal carotid artery) were used for plaque assessment, from the beginning of the cervical CCA to 30 mm after the origin of the internal carotid artery. After the placement, verification, and manual adjustment of a 10-mm wide measurement box, the images acquired were analyzed by the Arterial Measurement System II and automatic contour detection.

Plaque was defined as a focal structure that intruded into the arterial lumen by ≤0.5 mm or 50% of the value of neighboring CIMT or that measured ≥1.5 mm from the media-adventitia boundary to the intima-lumen boundary. Once a plaque was detected, plaque location and number were documented. Plaques were graded from 1 to 5: 1, none (total absence, thickening of CIMT might be seen); 2, minimal (minor isolated thickening); 3, moderate (moderate reduction in diameter by visible plaque); 4, severe (marked reduction in diameter by significant plaque); and 5, occlusion.

Validation of Methods

Quality of ultrasonographic acquisition was ensured by careful selection of vascular centers according to predetermined criteria (including type of ultrasound equipment) and by standardized training of all sonographers before their enrollment in a certification program. Only certified sonographers were allowed to perform carotid ultrasound examinations. Reader reproducibility studies were performed before the start of the reading process. In addition, reproducibility studies were performed before and during central batch reading to determine whether reproducibility was satisfactory throughout the study.

A technical evaluation of ultrasound equipment using a phantom was...
performed every year to control potential drift. Similar approaches were used for quality control of plaque reporting by the core laboratory and by the sonographers.

Outcome Analysis
The primary end point was annualized rate of change in common CIMT, which was based on measurements taken at baseline and 12, 24, and 36 months. Common CIMT was calculated as the average of the right and left mean values. Where only 1 side (right or left) was available at a visit, then only the values from this side were included in the analysis. The secondary outcome was the rate of emergent carotid plaques per year, based on measurements taken at the same time points as those for the primary end point.

Statistical Analysis
Baseline characteristics are presented as mean±SD for continuous variables and number of patients (percentages) for categorical variables. The full analysis set (intention to treat) comprised all patients with at least 1 baseline CIMT measurement and at least 1 postbaseline CIMT measurement at 12, 24, or 36 months who took at least 1 dose of study treatment. A linear mixed-effects regression model was used to investigate difference between the treatment groups for terms of the primary outcome. This model included fixed effects for the baseline common CIMT measure and treatment group. Time was defined as the time from the baseline to the follow-up measurement and was included in the model as a random effect. A time-by-treatment interaction term was included in the model to allow for different slopes/progression between the treatment groups. The rate of change in common CIMT was estimated, with corresponding 95% confidence interval (CI) for each treatment group in addition to the difference in progression between the treatment groups.

For the secondary outcome, a repeated-measures Poisson regression model was applied, with an offset for log(year). For each treatment group, the rate of emergent plaques (per year) was extracted, along with the rate ratio (Terutroban:placebo) and corresponding 95% CIs. Sensitivity analyses were performed for both the primary and secondary outcomes, with additional adjustments for age, sex, sonographer, and country. Subgroup analyses were performed for both the primary and secondary outcomes, with additional adjustments for age, sex, sonographer, and country. Subgroup analyses were performed for the primary outcome for subgroups of interest—age (<75 median), sex, country, risk factors, presence of hypertension, statin use, and baseline atherosclerosis level (CIMT/plaques; <2 median)—by testing the 3-way interaction between subgroup, time, and treatment group.

Statistical analyses were performed by the Robertson Center for Biostatistics, University of Glasgow, United Kingdom, and validated by the Biometry Division of Institut de Recherches Internationales Servier using SAS software (version 9.1). Assuming an expected SD of 0.11 mm in the rate of change in common CIMT and 10% annual rate of withdrawal, a sample size of 1100 patients was deemed necessary to detect a treatment-related change of 0.025 mm in common CIMT (ie, 0.01 mm per year) for a statistical power of ≥90% using a 2-sided test with a 5% type I error rate.15

Results
From 1274 patients invited, 1141 were included and randomized (592 Terutroban, 549 aspirin; Figure 1). The full analysis set was based on 101 patients (89% of the randomized set). Patients were excluded (64/592 Terutroban, 67/549 aspirin) because of a missing evaluation (baseline or postbaseline), refusal to continue participation, or not having taken the prescribed treatment.

Baseline characteristics are shown in Table 1. Mean age was 66.2±6.5 years, with 66% men and 99% white. Patients were overweight (body mass index, 27.7±4.2 kg/m²). Blood pressure was 138/80 mmHg. More than a quarter (28%) were current smokers. A large proportion had a history of hypertension (86%), hypercholesterolemia (54%), or had type II diabetes

<table>
<thead>
<tr>
<th>Table 1. Baseline Characteristics of the Studied Population</th>
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<tbody>
<tr>
<td>Terutroban Group (n=592)</td>
</tr>
<tr>
<td><strong>Demographic characteristics</strong></td>
</tr>
<tr>
<td>Men</td>
</tr>
<tr>
<td>Age, y</td>
</tr>
<tr>
<td>Ethnic origin</td>
</tr>
<tr>
<td>White</td>
</tr>
<tr>
<td>Asian</td>
</tr>
<tr>
<td>Black</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td><strong>Physical examination</strong></td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
</tr>
<tr>
<td><strong>Medical history, n (%)</strong></td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Previous ischemic stroke</td>
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<tr>
<td>Hypertriglyceridemia</td>
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<tr>
<td>Angina pectoris</td>
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<tr>
<td>Previous transient ischemic attack</td>
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<tr>
<td>Myocardial infarction</td>
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<tr>
<td>Peripheral artery disease</td>
</tr>
<tr>
<td><strong>Previous treatments, n (%)</strong></td>
</tr>
<tr>
<td>ACE inhibitor</td>
</tr>
<tr>
<td>Statin</td>
</tr>
<tr>
<td>Diuretic</td>
</tr>
<tr>
<td>β-Blocker</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
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<tr>
<td>Antidiabetic agent</td>
</tr>
<tr>
<td>Angiotensin receptor blocker</td>
</tr>
<tr>
<td><strong>Previous antiplatelet drugs</strong></td>
</tr>
<tr>
<td>Aspirin</td>
</tr>
<tr>
<td>Aspirin/dipyridamole combined</td>
</tr>
<tr>
<td>Clopidogrel</td>
</tr>
<tr>
<td>Dipyridamole</td>
</tr>
<tr>
<td>Ticlopidine</td>
</tr>
</tbody>
</table>

Values are mean±SD or numbers (%). ACE indicates angiotensin-converting enzyme; and BP, blood pressure.

*Treatment between qualifying event and randomization.
mellitus (29%). Sixty-two percent were receiving an angioten-
sin-converting enzyme inhibitor and 60% a statin. Almost all
patients received antithrombotic agents (97%) before the study,
the most common of which was aspirin (91%). There were no
significant differences in baseline characteristics between the
treatment groups, and characteristics were similar to that in the
main PERFORM study.10 Study and treatment duration were
comparable in the Terutroban and aspirin arms: 28±7 versus
28±6 months and 25±9 versus 25±9 months, respectively.
Reproducibility studies were performed with 58 images
acquired at baseline and 12 months read twice by 10 readers.
Inter-reader intraclass correlation coefficient for mean com-
mon CIMT was 0.83 (95% CI, 0.71–0.90). The intrareader
intraclass correlation coefficients for mean common CIMT
ranged from 0.86 to 0.97 (lower bound 95% CI, 0.78–0.98).
A further variability assessment (before central batch reading)
showed a good intrareader (intraclass correlation coefficient
>0.87) and a good inter-reader reproducibility (intraclass cor-
relation coefficient=0.83). As regard plaque reporting, similar
increases in a sample of plaque counts using the baseline and
12-month scans of 47 subjects were reported by core labora-
tory analysis and the sonographers (+14% versus +13%). A
second study in 38 patients with scans at baseline, 12 months,
and 24 months showed similar results.
Common CIMT (±SD) was 0.88±0.17 mm at baseline and
0.86±0.18 mm at study end (Table 2). In the Terutroban group,
the rate of change of common CIMT was 0.006 mm per year
(95% CI, –0.004 to 0.016 mm per year). In the aspirin group,
it was –0.005 mm per year (95% CI, –0.015 to 0.005 mm
per year). There was no significant difference between the
Terutroban and aspirin groups in the annualized rate of change
of common CIMT (0.011 mm per year; 95% CI, –0.003 to
0.025). Analysis with adjustments for age, sex, sonographer,
and country provided similar results.
At baseline, there were 351 patients (35%) with 1 to 2 carotid
plaques and 655 patients (65%) with ≥3 plaques. At study end
there were 386 patients (39%) with 1 to 2 emergent plaques
and 89 patients (9%) with ≥3 emergent plaques, that is, 52% of
the patients did not develop new plaques. At the first evaluation
of emergent carotid plaques (12 months), 65% of Terutroban
patients had no emergent plaques, 31% had 1 to 2 emergent
plaques, and 3% had ≥3 emergent plaques. In the aspirin group,
the corresponding percentages were 65%, 31%, and 4%. Over
time, there was no difference in the number of emergent carotid
plaques between the 2 treatment groups (rate ratio, 0.91; 95% CI,
0.77–1.07; Figure 2; Table 2). The analysis with adjustments
for age, sex, sonographer, and country provided similar results.
Specified subgroup analyses indicated no statistically sig-
nificant interactions, that is, the differences in rate of change
in common CIMT between the 2 treatment modalities did not
differ significantly across the studied subgroups as P values
ranged from 0.08 to 0.98.

Discussion
We showed that the TPR antagonist Terutroban 30 mg per
day, compared with aspirin 100 mg per day, did not provide
evidence of a significant vascular effect based on CIMT mea-
surements and plaque occurrence in patients with a history of
ischemic stroke or transient ischemic attacks, who were care-
fully treated with antithrombotic agents in a controlled best
medical care trial.
Our findings are in contrast with that of animal studies show-
ing a slowing down of atherosclerosis progression through

Table 2. Effect of Treatment on Main Carotid Atherosclerotic Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Terutroban</th>
<th>Aspirin</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common CIMT, mm</td>
<td>n=528</td>
<td>n=482</td>
<td>n=1010</td>
</tr>
<tr>
<td>Baseline, mean±SD</td>
<td>0.88±0.17</td>
<td>0.88±0.17</td>
<td>0.88±0.17</td>
</tr>
<tr>
<td>Last value, mean±SD</td>
<td>0.87±0.17</td>
<td>0.86±0.18</td>
<td>0.86±0.18</td>
</tr>
<tr>
<td>Rate of change, mm/y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Within treatment group (95% CI)</td>
<td>0.006 (~0.004 to 0.016)</td>
<td>~0.005 (~0.015 to 0.005)</td>
<td></td>
</tr>
<tr>
<td>Terutroban versus aspirin (95% CI)</td>
<td>0.011 (~0.003 to 0.025)</td>
<td></td>
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<tr>
<td>Emergent carotid plaques</td>
<td>n=511</td>
<td>n=476</td>
<td>n=987</td>
</tr>
<tr>
<td>Baseline, mean±SD</td>
<td>3.8±2.4</td>
<td>3.9±2.3</td>
<td>3.8±2.4</td>
</tr>
<tr>
<td>Last value, mean±SD</td>
<td>4.6±2.6</td>
<td>4.7±2.6</td>
<td>4.6±2.6</td>
</tr>
<tr>
<td>Emergent plaques at last visit</td>
<td>0.8±1.1</td>
<td>0.9±1.2</td>
<td>0.8±1.2</td>
</tr>
<tr>
<td>Rate of change, no./y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Within treatment group (95% CI)</td>
<td>0.41 (0.37 to 0.47)</td>
<td>0.45 (0.41 to 0.51)</td>
<td></td>
</tr>
<tr>
<td>Terutroban versus aspirin, rate ratio (95% CI)</td>
<td>0.91 (0.77 to 1.07)</td>
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</table>

Data are presented as numbers (%) and mean±SD. CI indicates confidence interval; and CIMT, carotid intima-media thickness.
TPR antagonism. In addition, Terutroban as a selective TPR antagonist, that is, a specific antagonist of the thromboxane A2 and prostaglandin endoperoxide receptors, has shown to improve flow-mediated dilatation of the brachial artery after a single administration in patients with coronary artery disease. Furthermore, coronary endothelial function has been shown to improve after Terutroban. Several studies indicated that endothelial dysfunction and atherosclerosis are closely related. Yet, in our well-treated population, no additional effect of Terutroban versus aspirin was seen. This finding was observed despite our large sample size (we are among the largest CIMT trials), good quality measurements (high reproducibility results comparable to other trials), and adequate statistical modeling.

In case of neutral results, one should always evaluate whether the finding may be because of increased measurement error. Our quality assurance and quality control program does not suggest that the common CIMT measurements and its reading procedure is of less quality than in other studies. Furthermore, our chosen outcome measurements are well established. One may argue whether the internal CIMT measurement would have been more suitable to use as a primary outcome instead of the common CIMT measurement. Some studies showed a stronger relationship for internal CIMT than for common CIMT with stroke. Yet, the issue whether the antiatherosclerotic effect of the intervention would be more pronounced in internal CIMT than in the common CIMT is unclear. From previous trials using blood pressure–lowering drugs or lipid-lowering drugs, it was unpredictable where the beneficial effect was most pronounced. So, we think the common CIMT was still appropriate, also given the generally accepted notion that in multicenter CIMT trials (we had 56 centers) higher precision and completeness can be achieved for the common CIMT measurements than for the internal CIMT measurements. There are several lines of evidence to suggest that the rate of change in CIMT over time is a good atherosclerosis end point. Also for plaques, recent evidence emerged to suggest that change over time can be readily and reliably assessed. Likewise a second ancillary study of PERFORM (748 patients included to investigate the evolution of MRI lesions) failed to demonstrate the progression of fluid attenuated inversion recovery imaged lesions, brain or hippocampal volumes, or emergent microbleeds. Whether both Terutroban and aspirin actually prevented the progression of brain lesions or atherosclerosis progression remains speculative. Yet, the design and performance of the PERFORM ancillary studies provided solid findings based on the large number of patients investigated. However, time course might have been too short to demonstrate significant differences, in particular because of effective control of risk factors of atherosclerosis and strict general medical management of patients in these recent trials.

Our findings are in line with the main results of the PERFORM study, that is, no difference in incidence rates of major cardiovascular outcomes across treatment modalities. Had we found a beneficial effect on atherosclerosis progression, we would have expected a beneficial effect of the treatment on event rates. As recently has been shown, results from trials using CIMT as primary outcome often mirror results from event trials.

In conclusion, compared with aspirin, Terutroban did not beneficially affect the progression of carotid atherosclerosis among well-treated patients with a history of ischemic stroke or transient ischemic attacks and an internal carotid stenosis <70%.

Appendix: PERFORM Vascular Ultrasound Study Investigators

Organization: This has been described elsewhere. The PERFORM Vascular Ultrasound Project was supervised by a committee comprising 5 members: M.G. Hennerici (Chairman), M.L. Bots, I. Ford, S. Laurent, and P.J. Touboul. Bioclinica, Leiden, The Netherlands, was responsible for the image analysis, processing, and reading as well as quality control.

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Belgium: V. Thijs
Canada: D. Selchen, D. Spence
Czech Republic: M. Bar, P. Kanovsky, I. Rektor, O. Skoda, D. Vaclavik
France: C. Lucas, T. Rosolacci, P. Trouillas
Germany: B. Griewling, M. Hennerici, A. Hetzel, M. Kaps, W. Koehler, J. Roether
Italy: C. Cappelletti, V. Di Piero, P. Prati, P. M. Rossini
The Netherlands: M.L. Bots, L.J. Kappelle
Poland: A. Czlonkowska, W. Kozubski, A. Kuczynska-Zardzewialy, H. Kwiecinsky
Portugal: A.V. Salgado
Russia: D. Butko, E. Gusev, P. Kamchatnov, S. Kotov, V. Parfenov, V. Skvortsova, L. Stakhovskaya
Sweden: B. Zvan
Switzerland: R.W. Baumgartner, L. Hirt

Acknowledgments

We thank the investigators and patients who contributed to this study, as well as Rudy Meijer of Bioclinica, Leiden, The Netherlands. Dr Ford had full access to all of the data and takes responsibility for the integrity and accuracy of the data analysis. Drs Hennerici, Bots, Ford, Laurent, and Touboul were responsible for study design. The work is supported by Servier. The sponsor participated in discussions regarding the design and conduct of the study and provided logistical support during the trial. Monitoring of the study and maintenance of the trial was performed by a contract research organization under contract with the sponsor. Collection, management, and analysis of the data were performed by the sponsor and the contract research organization under contract with the sponsor. The article was prepared by the author group. The sponsor was permitted to review the article and suggest changes, but the final approval of content was exclusively retained by the authors.

Sources of Funding

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Disclosures

Drs Bots, Ford, Hennerici, and Lloyd received honoraria and research grants from Servier. Drs Touboul and Laurent report a consultancy relationship with Servier. Dr Touboul has an employment with Intelligence in Medical Technologies, Paris, France. The other authors report no conflicts.
References
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