REVIEW

Treating coronary artery disease in patients with a history of cerebrovascular disease

Prise en charge des patients coronariens avec un antécédent de maladie cérébrovasculaire

Gregory Ducrocq\textsuperscript{a,b,\textdagger}, Philippe Gabriel Steg\textsuperscript{a,b,c,d}

\textsuperscript{a} French Alliance for Cardiovascular Clinical Trials (FACT), département hospitalo-universitaire FIRE, AP–HP, hôpital Bichat, Paris, France
\textsuperscript{b} LVTs, Inserm U-1148, Paris, France
\textsuperscript{c} Université Paris-Diderot, Sorbonne Paris Cité, Paris, France
\textsuperscript{d} National Heart and Lung Institute, ICMS, Royal Brompton hospital, London, UK

Received 25 June 2015; accepted 26 June 2015
Available online 12 September 2015

Summary  Patients with coronary artery disease and a history of stroke account for as many as one in eight of all patients with coronary artery disease, and they are at higher risk of ischaemic events than patients with ‘lone’ coronary artery disease. It is therefore tempting to increase the potency of antithrombotic treatment in this patient subset. However, these patients are also at greater risk of intracranial haemorrhage. In recent trials of new antithrombotic agents in acute coronary syndromes, patients with a history of cerebrovascular disease derived no clinical benefit from (and were even harmed by) the potent novel antithrombotic agents, with an increased risk of intracranial haemorrhage. However, this risk did not appear to be uniform: it was higher in patients with a history of stroke than in those with a history of transient ischaemic attack, and appeared to be largely confined to the first year after stroke/transient ischaemic attack. Specific strategies to optimize the benefit/risk ratio of antithrombotic agents in this relatively common patient group should be developed and evaluated.

\textcopyright{} 2015 Elsevier Masson SAS. All rights reserved.

Abbreviations: ACS, Acute coronary syndrome; CAD, Coronary artery disease; CI, Confidence interval; HR, Hazard ratio; ICH, Intracranial haemorrhage; TIA, Transient ischaemic attack; TIMI, Thrombolysis in myocardial infarction.

\textdagger{} Corresponding author. Inserm U-1148 and cardiology department, hôpital Bichat, 46, rue Henri-Huchard, 75877 Paris cedex 18, France.

E-mail address: gregducrocq@hotmail.com (G. Ducrocq).

http://dx.doi.org/10.1016/j.acvd.2015.06.003
1875-2136/\textcopyright{} 2015 Elsevier Masson SAS. All rights reserved.
Background

Atherothrombosis is a generalized disease that often involves not only the coronary arteries, but also other arterial beds. For that reason, patients presenting with several atherothrombosis locations are not uncommon. Among them, patients presenting with coronary artery disease (CAD) and a history of cerebrovascular disease are of particular interest, because they occur frequently and present a therapeutic conundrum.

Patients with CAD and cerebrovascular disease: a frequent clinical problem

A history of cerebrovascular disease (including stroke or transient ischaemic attack [TIA]) is not uncommon in patients with CAD. In a cohort of more than 26,000 patients with CAD enrolled in the REACH registry of atherothrombosis, 4460 patients (approximately 17% of the CAD population) had a history of cerebrovascular disease (stroke or TIA) [1]. In the GRACE registry of acute coronary syndromes (ACSs), patients with a history of stroke constituted 8.25% of the overall population [2]. Cerebrovascular disease is therefore a common condition in patients with stable or unstable CAD.

Characteristics of patients with CAD and cerebrovascular disease

In the REACH registry, CAD patients with cerebrovascular disease were older, more frequently female and more likely to have a history of diabetes, hypertension or atrial fibrillation than patients with CAD alone. Overall, patients with a history of both CAD and cerebrovascular disease had a higher baseline risk of recurrent cardiovascular and bleeding events [1].

Risk of ischaemic events in patients with CAD and cerebrovascular disease

CAD patients with a history of cerebrovascular disease have worse clinical outcomes than patients without a history of cerebrovascular disease. In the GRACE registry, ACS patients with a history of stroke had dramatically higher hospital and 6-month mortality rates than patients without a history of stroke (8.9% vs 4.5% and 9.3% vs 3.9%, respectively); these differences persisted after adjustment for baseline characteristics [2]. In a pooled analysis of five French multicentre acute myocardial infarction registries, including nearly 10,000 patients (the Alliance project), multivariable analysis showed that a history of cerebrovascular disease was an independent factor for hospital mortality [3]. In stable patients, the same observation was made in the REACH registry: patients with a history of stroke/TIA had a higher rate of 5-year all-cause death (17.8% vs 11.2%) — mainly driven by cardiovascular death (12.2% vs 7.1%) — and cardiovascular events (24.9% vs 13.3% for cardiovascular death, myocardial infarction or stroke) — mainly driven by stroke (13.1% vs 4.1%) — compared with patients with CAD alone. These differences persisted after adjustment for differences in baseline characteristics [1].

Risk of intracranial haemorrhage in patients with CAD and cerebrovascular disease

As patients with CAD and previous stroke/TIA are at higher risk of ischaemic events, it is tempting to increase the potency of antithrombotic therapy in these patients. However, in several recent trials of new antithrombotic agents during or after ACS, patients with a history of cerebrovascular disease derived no benefit from (and in some cases were clearly harmed by) increasing the potency of antithrombotic therapy, while the rest of the patients (i.e. patients with ACS but without a history of cerebrovascular disease) derived benefit (see Table 1).
<table>
<thead>
<tr>
<th>Trial</th>
<th>Population</th>
<th>Study drug</th>
<th>Ischaemic endpoint</th>
<th>Bleeding endpoint</th>
<th>Overall population</th>
<th>Previous stroke/TIA</th>
<th>Bleeding events</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRACER</td>
<td>ACS</td>
<td>Vorapaxar</td>
<td>Death from vascular cause + MI + stroke + recurrent ischaemia with hospitalization + urgent coronary revascularization</td>
<td>Moderate or severe bleeding according to GUSTO classification&lt;sup&gt;a&lt;/sup&gt;</td>
<td>No significant reduction (HR 0.92; P = 0.07)</td>
<td>No significant interaction (P = 0.795)</td>
<td>No significant interaction (P = 0.771)</td>
</tr>
<tr>
<td>TRA-2P</td>
<td>Secondary atherothrombosis prevention</td>
<td>Vorapaxar</td>
<td>Death from vascular causes + MI + stroke</td>
<td>Moderate or severe bleeding according to GUSTO classification&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Reduction (HR 0.87; P &lt; 0.001)</td>
<td>Increase (HR 1.66; P &lt; 0.001); increase in ICH, 1% vs 0.5% (P &lt; 0.001)</td>
<td>No significant interaction (P = 0.81)</td>
</tr>
<tr>
<td>TRITON</td>
<td>ACS</td>
<td>Prasugrel</td>
<td>Death from CV cause + non-fatal MI + non-fatal stroke</td>
<td>TIMI major bleeding not related to CABG</td>
<td>Reduction (HR 0.81; P = 0.001)</td>
<td>Increase (HR 1.32; P = 0.03)</td>
<td>Increase (HR 2.46; P for interaction = 0.22)</td>
</tr>
<tr>
<td>APPRAISE-2</td>
<td>ACS</td>
<td>Apixaban</td>
<td>CV death + MI + ischaemic stroke</td>
<td>TIMI major bleeding</td>
<td>No significant reduction (HR 0.95; P = 0.51)</td>
<td>Increased risk of major bleeding (HR 2.59; P &lt; 0.001) Increase 2.1% vs 0.6% (P &lt; 0.001); including ICH, 0.6% vs 0.2 (P = 0.009)</td>
<td>No significant interaction (P = 0.10)</td>
</tr>
<tr>
<td>ATLAS ACS-2</td>
<td>ACS</td>
<td>Rivaroxaban</td>
<td>CV death + MI + stroke</td>
<td>TIMI major bleeding not related to CABG</td>
<td>Reduction (HR 0.84; P = 0.008)</td>
<td>No significant increase (P = 0.43)</td>
<td>No significant interaction (P = 0.84)</td>
</tr>
<tr>
<td>PLATO</td>
<td>ACS</td>
<td>Ticagrelor</td>
<td>CV death + MI + stroke</td>
<td>Major bleeding: fatal bleeding + ICH + intrapericardial bleeding with tamponade + haemorrhagic shock + decline in Hb ≥ 5 g/dL + transfusion ≥ 4 RBC units</td>
<td>Reduction (HR 0.84; P = 0.001)</td>
<td>No significant increase (P = 0.43)</td>
<td>No significant interaction (P = 0.84)</td>
</tr>
</tbody>
</table>


<sup>a</sup> Therefore includes intracranial bleeding.
The TRACER trial, evaluating the addition of vorapaxar — a PAR-1 antagonist — to dual antiplatelet therapy with aspirin and clopidogrel in patients with ACS, found an increased risk of major bleeding, including ICH (intracranial haemorrhage) [4]. A subgroup analysis showed a trend towards an increased risk of bleeding in patients with a history of stroke. The TRA-2P trial evaluated vorapaxar in a secondary prevention setting [5]. In this trial, vorapaxar reduced the rate of the primary ischaemic composite endpoint compared with placebo, but with a significant increase in bleeding, including ICH, in patients with and without a history of stroke. However, the absolute rate of ICH was substantially higher in patients with a history of stroke. Subgroup analysis revealed that, in contrast to the overall population, there was no benefit derived from adding vorapaxar in the subgroup of patients with previous cerebrovascular disease. In both of these trials, because of an excess risk of ICH in an interim analysis, the Data and Safety Monitoring Board decided to withdraw treatment with vorapaxar from patients with a history of cerebrovascular disease. While vorapaxar was approved for secondary prevention after myocardial infarction, both the Food and Drug Administration and the European Medicines Agency have designated history of stroke/TIA as a contraindication [6].

In the TRITON-Thrombolysis in Myocardial Infarction (TIMI) 38 trial, comparing prasugrel with clopidogrel in ACS patients treated with percutaneous coronary intervention, prasugrel reduced the rate of ischaemic events, but at a price (an increased risk of major bleeding in the overall population) [7]. However, a post-hoc analysis identified that patients with previous stroke or TIA derived net clinical harm from prasugrel (hazard ratio [HR] 1.54, 95% confidence interval [CI] 1.02 to 2.32; \( p = 0.04 \)), contrasting with the overall results (HR 0.81, 95% CI 0.73 to 0.90; \( p < 0.001 \)); this was mainly due to excess bleeding, including ICH, in this subgroup. Moreover, there was a significant interaction between a history of cerebrovascular events and the net clinical benefit of prasugrel over clopidogrel. Again, a history of stroke/TIA is a contraindication to prasugrel treatment [6].

The PLATO trial demonstrated a benefit for ticagrelor versus clopidogrel in ACS patients in terms of reducing the risk of the primary composite ischaemic outcome (cardiovascular death, myocardial infarction or stroke) [8]. In the subgroup of patients with previous stroke/TIA, efficacy was consistent with that seen in the overall trial, with even a marked decrease in all-cause mortality at 1 year with ticagrelor compared with clopidogrel (7.9% vs 13.0%) [9]. However, in contrast to the increased risk seen in other trials, rates of major bleeding — according to the PLATO or TIMI definitions — were not increased with ticagrelor compared to clopidogrel. Note, however, that there were too few ICHs to definitively rule out an increase in the risk of ICH with ticagrelor [10]. In addition, in the overall trial population, there was a trend toward more ICH with ticagrelor than with clopidogrel (0.3% vs 0.2%; \( p = 0.06 \)). The SOCRATES trial (ClinicalTrials.gov identifier NCT01994720) will compare ticagrelor initiated within 24 hours after stroke or high-risk TIA onset with aspirin; it will provide important information on the safety of ticagrelor in the early weeks following stroke or TIA [11].

The APPRAISE-2 trial, evaluating a high dose (5 mg twice daily) of apixaban, a factor Xa inhibitor, in addition to standard therapy after recent ACS, was terminated prematurely because of an increase in major bleeding events with apixaban without a significant reduction in recurrent ischaemic events [12]. In patients with previous stroke, apixaban was associated with worse outcomes regarding the primary efficacy endpoint (\( P \) for interaction = 0.08) and an increase in TIMI major bleeding, although this was not significant (HR 5.44 for patients with previous stroke vs 2.27 for patients without; \( P \) for interaction = 0.31).

Rivaroxaban, another factor Xa inhibitor, was evaluated on top of dual antiplatelet therapy in the ATLAS ACS-2 trial [13]. In this trial, which included 15,526 patients with a recent ACS, a low dose of rivaroxaban (2.5 mg or 5 mg twice daily) reduced the risk of the primary composite endpoint (8.9% vs 10.7%, HR 0.84, 95% CI 0.74 to 0.96; \( P = 0.008 \)), but increased the risk of major bleeding (2.1% vs 0.6%; \( P < 0.001 \)) and ICH (0.6% vs 0.2%; \( P = 0.009 \)) in the overall trial population. There were too few bleeding events in the subgroup of patients with a history of stroke/TIA (four events in the rivaroxaban arm; none in the placebo arm) to allow a meaningful comparison.

This increased risk of ICH in patients with CAD and a history of stroke was also seen in observational studies, such as the REACH registry [1]. In this registry, patients with CAD and a history of stroke had a higher risk of ICH (adjusted HR for non-fatal haemorrhagic stroke 1.76, 95% CI 1.00 to 3.08; \( P = 0.05 \)). When the analysis was stratified according to antiplatelet therapy at admission, the increased risk of non-fatal haemorrhagic stroke was particularly high in patients receiving dual antiplatelet therapy. In this subgroup, the adjusted HR of non-fatal haemorrhagic stroke associated with cerebrovascular disease history was 5.21 (95% CI 1.24 to 21.90), whereas there was no significant increase in patients receiving no or single antiplatelet therapy.

Patients with CAD and a history of cerebrovascular disease therefore have a high risk of recurrent ischaemic events. However, there is a consistent pattern across trials — with the possible exception of ticagrelor in the PLATO trial — of a disproportionate increase in ICH when the potency of antithrombotic therapy is increased.

The **risk of ICH is not uniform in all patients with cerebrovascular disease**

The increase in bleeding risk does not appear to be uniform across all patients with cerebrovascular disease. An analysis from the REACH registry demonstrated that patients with CAD and a history of stroke had a higher risk of ICH. The sensitivity analysis, excluding patients with TIA only, made a similar observation in patients with a history of stroke only. Conversely, patients with a history of TIA alone had a lower increase in stroke rate and no difference in death rate. It appears, therefore, that the risk of ICH is greater for patients with a history of stroke than for those with a history of TIA [1].

The risk of ICH also varies according to the time elapsed since a previous stroke/TIA. In the REACH registry [1], the excess risk of non-fatal haemorrhagic stroke in patients with
a history of stroke/TIA compared with those without a history of stroke/TIA decreased with the time elapsed between cerebrovascular disease onset and enrolment. The increased risk appeared to be confined to the first year following a stroke or TIA (adjusted HR 3.03, 95% CI 1.51 to 6.08), whereas beyond 1 year, the risk was not increased (adjusted HR 1.15, 95% CI 0.53 to 2.47). Overall, the risk of haemorrhagic stroke was greater in the first year after a stroke/TIA than later (HR 2.64, 95% CI 1.04 to 6.69; \( P = 0.041 \)).

To take into account these differences in ICH risk, we have proposed an algorithm for ACS patients (Fig. 1). In patients without a history of stroke/TIA, we suggest ticagrelor or prasugrel as first-line therapy, in agreement with the European Society of Cardiology guidelines [14]. In patients with a history of stroke/TIA, prasugrel is contraindicated [7]. Based on the results of the REACH registry analysis [1], and the mortality benefit provided by ticagrelor compared with clopidogrel in this population [9], we suggest using ticagrelor as first-line therapy in patients with a history of stroke/TIA > 1 year previously. In patients with a history of stroke within the previous year, based on the results of the REACH analysis, we suggest using clopidogrel as first-line therapy until additional information about ticagrelor safety becomes available [11].

**Conclusions**

Patients with CAD and a history of stroke are a relatively large patient subset (accounting for as many as 8–17% of CAD patients). These patients are at higher risk of ischaemic events, but also ICH. In this population, increasing the potency of antithrombotic treatment is generally associated with an increased risk of ICH. However, the increase in bleeding risk does not appear to be uniform in all patients with cerebrovascular disease: it is greater for patients with a history of stroke (compared with a history of TIA), and in the first year after stroke. Specific strategies to optimize the management of this group of patients should be developed and evaluated.

**Disclosure of interest**

G. D. Speaking/consulting for the companies AstraZeneca, Lilly and MSD.

P. G. S. Research grant from the companies Sanofi, Servier. Speaking/consulting for the companies Amarin, AstraZeneca, Bayer, Boehringer-Ingelheim, BMS, Daiichi-Sankyo, GSK, Lilly, Medtronic, Otsuka, Pfizer, Roche, Sanofi, Servier and the Medicines Company. Stockholding in the company Aterovax.

**References**

Coronary artery disease and cerebrovascular disease


