Management of Antithrombotic Therapy in Post-Myocardial Infarction Patients

Subjects: Neurosciences

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The association between atrial fibrillation (AF), acute coronary syndrome (ACS), and stroke is a complex scenario in which the assessment of both thrombotic and hemorrhagic risk is necessary for scheduling an individually tailored therapeutic plan.

Keywords: acute ischemic stroke ; atrial fibrillation ; myocardial infarction

1. Management of Antithrombotic Therapy in Post-Myocardial Infarction Patients with Stroke with and without Atrial Fibrillation: Lessons from Clinical Trials

Although there is a strong growing body of evidence for the management of patients with pre-existing atrial fibrillation (AF) presenting with acute myocardial infarction (MI) [1], data on stroke prevention after acute MI are more limited, particularly for the patient without AF [2].

Patients with acute coronary syndrome (ACS) and previous stroke/TIA have a higher risk of ischemic events, therefore, safely empowering antithrombotic therapy is desirable in these populations in order to balance the bleeding and thrombotic risks. Recently, new antithrombotic drugs, during or after ACS, were tested in several clinical trials However, in most of them, the cerebrovascular bleeding risk exceeded the antithrombotic benefit.

2. Clinical Trials in Combined Antithrombotic Drugs in Coronary Artery Disease (CAD) Patients

The TRACER trial [3] evaluated the association between vorapaxar (PAR-1 antagonist) and dual antiplatelet therapy (DAPT) with aspirin and clopidogrel in patients with ACS. In the study population, the combination of vorapaxar with standard therapy did not significantly change the primary composite endpoint of cardiovascular death, myocardial infarction, stroke, recurrent ischemia with urgent re-hospitalization, or coronary revascularization, but led to an increased risk of major bleeding, including intracranial hemorrhage (ICH), mainly in patients with a history of stroke.

In a secondary prevention setting, patients with a history of MI, acute ischemic stroke (AIS), or peripheral arterial disease (PAD) were challenged with 2.5 mg of vorapaxar. The TRA 2P–TIMI 50 trial [4] was discontinued in patients with a history of stroke owing to the risk of intracranial hemorrhage. However, vorapaxar reduced the risk of cardiovascular death or ischemic events in patients with stable atherosclerosis who were receiving standard therapy (aspirin and/or clopidogrel) and is recommended in patients with MI and PAD, while previous stroke (TIA/AIS and ICH) is a contraindication. Similarly, in the TRITON-Thrombolysis in Myocardial Infarction (TIMI) 38 trial [5], prasugrel was shown to reduce the rate of ischemic events and significantly increased the risk of ICH in patients with previous stroke or TIA; hence, a history of cerebrovascular events contraindicates prasugrel therapy. The TRITON-Thrombolysis in Myocardial Infarction (TIMI) 38 trial compared prasugrel vs. clopidogrel in patients with ACS treated by percutaneous coronary intervention. A post-hoc analysis showed that prasugrel reduced the rate of ischemic events, but in patients with previous stroke or TIA, it increased the risk of major bleeding (HR: 0.81, 95% CI: 0.73 to 0.90; $p < 0.001$). Indeed, a history of stroke/TIA represents a contraindication to prasugrel treatment [6].

Ticagrerol has been extensively studied in the cardiovascular patient population. In the PLATO [7] trial, ticagrerol, compared to clopidogel, reduced the risk of the primary composite ischemic outcome (cardiovascular death, MI, or stroke) in patients with ACS without significantly increasing the risk of ICH in subjects with a history of non-hemorrhagic stroke. The SOCRATES and the THALES trials were conducted in patients with non-cardioembolic, non-severe acute ischemic

stroke, or high-risk transient ischemic attack. In the first study, ticagrelor monotherapy was not superior to aspirin in reducing the rate of stroke, myocardial infarction, or death at 90 days; however, in patients (about 25% of the trial population) with ipsilateral atherosclerotic stenosis, ticagrelor was superior to aspirin (6.7% vs. 9.4%, HR: 0.68 (0.53–0.88) p = 0.003), whereas in those with no ipsilateral stenosis, this effect was not observed [8][9]. In the THALES trial, ticagrelor combined with aspirin was superior to aspirin alone in patients with TIA and minor stroke for the prevention of stroke or death (5.5% vs. 6.6%, HR: 0.83 (0.71–0.96), p = 0.015) [9]. In patients with ipsilateral atherosclerotic stenosis, the absolute event rate for stroke or death within 30 days was higher in patients on aspirin alone (10.9%) than in patients on ticagrelor added to aspirin (3.0%) compared to patients without ipsilateral stenosis (5.3% and 0.5%, respectively). This is concordant with prior studies suggesting that atherosclerotic disease carries a greater risk than other stroke subtypes without stenosis among patients with TIA or minor ischemic stroke events on aspirin. Based on the results of the SOCRATES and THALES studies, treating patients with atherosclerotic stenosis with combination therapy, ticagrelor, and aspirin, could produce a clinically significant reduction in the relative and absolute risks of stroke and death compared to aspirin alone.

The rationale for combining anticoagulation and antiplatelet therapy for the acute treatment of ACS patients is well established. The rupture of atherosclerotic plaques is responsible for most acute coronary thrombosis events, and acute thrombus formation depends on both platelet aggregation and the coagulation cascade [10]. Accordingly, the current guidelines for the management of ACS recommend acute antiplatelet and anticoagulant therapy for hospitalized ACS patients regardless of whether or not percutaneous coronary intervention (PCI) is performed. As there is also evidence that thrombin generation persists for several months after ACS, combining oral antithrombin as part of a “dual pathway” can reduce the risk of recurrent thrombotic events and improve outcomes.

Several clinical trials in the 1990s—testing the association of ASA and warfarin—demonstrated lower odds of death, MI, or stroke compared with those observed with aspirin alone, but with a significant increase in major bleeding. Therefore, anticoagulation was never integrated into the standard of care for post-ACS patients who have no other indication for chronic anticoagulation.

In recent years, the APPRAISE-2 (Apixaban for Prevention of Acute Ischemic Events 2) [11] and the ATLAS ACS 2-TIMI 51 (Anti Xa Therapy to Lower Cardiovascular Events in Addition to ASA with or without Thienopyridine Therapy in Subjects with Acute Coronary Syndrome—Thrombolysis in Myocardial Infarction) [12] phase III clinical trials investigated the use of direct oral anticoagulants (apixaban and rivaroxaban, respectively) in the post-acute treatment of ACS. Both trials demonstrated a significant increase in major bleeding with their respective factor Xa inhibitors compared with dual antiplatelet therapy. In the latter study, in patients with previous stroke, apixaban was associated with worse outcomes regarding the primary efficacy endpoint (p for interaction = 0.08).

More encouraging results were shown by the COMPASS trial (Cardiovascular Outcomes for People Using Anticoagulation Strategies) [13], which investigated the use of rivaroxaban plus aspirin vs. aspirin monotherapy among patients with stable atherosclerotic vascular disease, 91% of whom had stable coronary artery disease. The composite primary outcome of cardiovascular death, stroke, or MI occurred less often among patients randomly assigned to 2.5 mg of rivaroxaban twice daily plus aspirin than among patients treated with aspirin alone (83 (0.9% per year) vs. 142 (1.6% per year); hazard ratio (HR), 0.58; 95% CI, 0.44–0.76). Ischemic/uncertain strokes were reduced by nearly half by the combination in comparison with aspirin alone (68 (0.7% per year) vs. 132 (1.4% per year); HR, 0.51; 95% CI, 0.38–0.68; $p < 0.0001$). No significant difference in the occurrence of stroke in the rivaroxaban-alone group in comparison with that for aspirin was noted (HR, 0.82; 95% CI, 0.65–1.05). Although major bleeding was higher in the rivaroxaban-plus-aspirin group (27 vs. 10; HR, 2.70; 95% CI, 1.31–5.58; p = 0.005), there was no increase in major/fatal bleeding or ICH (HR, 1.06; 95% CI, 0.72–1.56; p = 0.76; interaction p = 0.19).

The results of the COMPASS trial raise the possibility that long-term dual pathway inhibition by low-dose anticoagulation combined with low-dose antiplatelet therapy may be acceptably safe and substantially more effective than single pathway inhibition by antiplatelet therapy alone in preventing recurrent vascular events among patients with a history of atherosclerotic TIA and ischemic stroke.

From a stroke risk point of view, fatal and intracranial hemorrhage risk appear to be increased when a third antiplatelet medication (e.g., P2Y12 inhibitor) is included. The anticoagulant drug and dosage selection are also crucial: full-dose anticoagulation in the APPRAISE-2 study (apixaban at 5 mg twice daily) was associated with higher rates of major bleeding. However, very low doses of rivaroxaban (2.5 mg twice daily) were, overall, safe and efficacious in the COMPASS study.

As mentioned above, it is estimated that atrial fibrillation develops in up to 20% of patients with ACS, and these patients have higher stroke rates and in-hospital mortality than patients without atrial fibrillation. Their secondary prevention strategy is a complex clinical management issue that involves balancing thrombotic and bleeding risks.

3. Clinical Trials in Combined Antithrombotic Drugs in Atrial Fibrillation (AF) and Coronary Artery Disease (CAD)

A number of randomized controlled trials in acute MI patients with AF have assessed the effects of direct oral anticoagulants as an add-on therapy to dual antiplatelet therapy with aspirin and clopidogrel [14].

The WOEST (What Is the Optimal Antiplatelet and Anticoagulant Therapy in Patients with Oral Anticoagulation and Coronary Stenting) trial compared DAPT and warfarin with clopidogrel (at a dose of 75 mg a day) and warfarin [15]. Without aspirin, fewer bleeding complications were noted.

The PIONEER AF-PCI (Open-Label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects with Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention) trial, in which patients were randomly assigned to one of two rivaroxaban strategies (low-dose rivaroxaban plus a P2Y12 inhibitor or very-low-dose rivaroxaban plus a P2Y12 inhibitor and low-dose aspirin) or triple therapy with warfarin, showed a lower rate of bleeding with each of the rivaroxaban treatment strategies than with triple therapy [16]. Moreover, the RE-DUAL PCI (Randomized Evaluation of Dual Antithrombotic Therapy with Dabigatran versus Triple Therapy with Warfarin in Patients with Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention) trial randomly assigned patients to receive dabigatran with a P2Y12 inhibitor or warfarin-based triple therapy [17].

The AUGUSTUS (Antithrombotic Therapy after Acute Coronary Syndrome or PCI in Atrial Fibrillation) trial evaluated the independent effects of the oral anticoagulant apixaban and aspirin in patients with atrial fibrillation and a recent acute coronary syndrome or PCI (within the previous 14 days) [18]. Apixaban resulted in a lower bleeding rate than warfarin, and aspirin led to a higher bleeding rate than the placebo. The ENTRUST-AF PCI (Edoxaban Treatment Versus Vitamin K Antagonist in Patients with Atrial Fibrillation Undergoing Percutaneous Coronary Intervention) trial provided support for another DOAC as an option for patients with atrial fibrillation requiring antiplatelet therapy after PCI [19].

The above-mentioned studies demonstrated that it is safe to treat patients with an increased risk for bleeding with anticoagulation (warfarin studied in WOEST, rivaroxaban studied in PIONEER AF-PCI, dabigatran in RE-DUAL PCI, and edoxaban in ENTRUST-AF PCI) and P2Y12-inhibitor monotherapy. For patients with AF undergoing PCI, evidence suggests a regimen of DOACs plus a P2Y12 inhibitor was associated with fewer bleeding complications, including intracranial bleeding, without a significant difference in ischemic events compared with VKA plus DAPT. From a stroke point of view, it is important to highlight that all these studies have cerebrovascular events among the exclusion criteria; in this sense, the most restrictive was the PIONEER AF PCI, excluding all patients with a history of TIA or stroke, whereas the less restrictive was the RE-DUAL PCI trial, with stroke within 1 month among the exclusion criteria. Both the WOEST and ENTRUST-AF PCI trials did not enroll subjects with a history of ICH, and intracerebral vascular abnormalities are considered to be a significant risk for major bleeding.

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