

# In search for an optimal antithrombotic regimen in patients with atrial fibrillation undergoing stenting

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Patients treated with coronary stenting are at an increased risk for thrombotic events such as stent thrombosis, myocardial infarction, and ischemic stroke. Dual antiplatelet therapy (DAPT) with aspirin and a P2Y<sub>12</sub> receptor inhibitor is the current standard of care due to an enhanced antiplatelet effect as compared with monotherapy with either agent. The optimal treatment duration and the choice of P2Y<sub>12</sub> receptor inhibitor (clopidogrel vs ticagrelor or prasugrel) are dependent on the severity of the disease (stable coronary artery disease [CAD] vs acute coronary syndrome [ACS]), stent type, and bleeding risk.<sup>1</sup> Targeting the thrombin pathway with a vitamin K antagonist (VKA) has been shown to be more effective in preventing reinfarction and stroke than aspirin + clopidogrel in patients with atrial fibrillation (AF).<sup>2</sup> However, nearly 20% to 30% of patients have concomitant AF and CAD, and 5% to 15% of these patients require percutaneous coronary intervention (PCI) with stenting.<sup>3</sup> These patients are at significant risk for morbidity and mortality.<sup>4</sup> Recommended treatments aim to reduce platelet-dependent thrombotic events and coagulation-dependent cardioembolic events in these patients by targeting both pathways simultaneously, otherwise known as triple (TT) or double (DT) antithrombotic therapy. However, TT poses a significant challenge due to a higher number of hemorrhagic events.

Several recent trials addressed this issue with different strategies: 1) DAPT + VKA compared with clopidogrel + VKA<sup>5</sup>; 2) 6 weeks of DAPT + VKA compared with 6 months of DAPT + VKA<sup>6</sup>; 3) low-dose rivaroxaban (15 mg once daily) + P2Y<sub>12</sub> inhibitor for 12 months compared with very-low-dose rivaroxaban (2.5 mg twice

daily) + DAPT for 1, 6, or 12 months compared with VKA + DAPT for 1, 6, or 12 months<sup>7</sup>; 4) VKA + P2Y<sub>12</sub> inhibitor (clopidogrel or ticagrelor) + aspirin (for 1 to 3 months) compared with dabigatran (110 mg or 150 mg twice daily) + P2Y<sub>12</sub> inhibitor (clopidogrel or ticagrelor)<sup>8</sup>; 5) P2Y<sub>12</sub> inhibitor + apixaban or VKA with and without aspirin.<sup>9</sup> Of note, these studies focused on demonstrating better safety outcomes and none were sufficiently powered to assess efficacy. A recent consensus document stated that an initial short course of TT should be used in most patients with AF undergoing PCI, depending on presentation (ACS vs non-ACS), stroke risk compared with bleeding risk, and procedural considerations (eg, stent type, disease severity). It is also recommended that TT should be followed by an oral anticoagulant plus a single antiplatelet agent (clopidogrel or, alternatively, aspirin) with preference for direct oral anticoagulants (DOACs) over VKAs. Among these patients, stroke and bleeding risk must be assessed using the CHA<sub>2</sub>DS<sub>2</sub>-VASC and HAS-BLEED scores, respectively.<sup>10</sup>

A meta-analysis by Grajek et al<sup>11</sup> published in this issue of *Kardiologia Polska (Kardiol Pol)* included 9931 patients from the 5 recent randomized clinical trials discussed above. The authors reported that CHA<sub>2</sub>DS<sub>2</sub>-VASC score values for stroke were similar, HAS-BLEED score values did not differ significantly with index values ranging between 2.7 to 3, and more than 90% of patients received clopidogrel. They showed a similar rate of major adverse cardiac events (MACEs) between DT and TT arms (9% vs 8.7%, respectively; odds ratio, 1.02; 95% CI, 0.86–1.21). As expected, the rate of bleeding complications (combination of major and minor bleeding events)

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was found to be significantly lower in DT than in TT arm (12.1% vs 21%, respectively; odds ratio, 0.54; 95% CI, 0.46–0.63). The authors conclude by emphasizing the need for a wider use of DT over TT in patients with AF undergoing stenting, which is in line with recent guideline recommendations.<sup>12</sup>

Grajek et al<sup>11</sup> address a clinically relevant issue about the choice of combination agents in patients with AF undergoing coronary stenting. The results of this analysis should be interpreted with caution due to some caveats. The analyses of the efficacy endpoint (MACE reduction) and safety endpoint (hemorrhagic complications) had 33% and 69% heterogeneity, respectively. Although the random-effects model was used to attenuate the effects of significant heterogeneity, values greater than 25% indicate that the combined patient populations from different clinical trials differed significantly. Heterogeneity was likely attributable to the differences in the definitions of major bleeding (International Society on Thrombosis and Haemostasis vs Thrombolysis in Myocardial Infarction vs clinically significant bleeding) and MACE in the individual studies in addition to differences between patient populations. The wide range of the follow-up duration from 6 months to 14 months could have potentially affected the sensitivity of detecting MACE and hemorrhagic events. A patient-level meta-analysis with an hemorrhagic outcome combining major and minor bleeding events associated with a change of antithrombotic agents could yield more clinically significant results.

At this time, the optimal antithrombotic therapy strategy among patients with AF undergoing stenting remains unclear. The underlying pathobiology of AF is less known compared with CAD. First, a careful assessment of thrombotic, embolic, and bleeding risk is critical, since the underlying pathobiology of these events differs with respect to the relative contribution of platelet function and thrombin pathways. With regard to that, most of the current risk scores are based mainly on demographic and clinical variables without an objective laboratory assessment of platelet and thrombin pathways. Second, personalization of therapy—the choice and combination of antithrombotic agents—that is based on the relative contribution of each pathway deserves further study. There is sufficient high-quality evidence from randomized controlled trials and meta-analyses to support DT as compared with TT regarding safety outcomes but not for the individual components of MACE.<sup>12</sup> In the initial period after stenting (up to 3 months) where thrombotic risk is high, TT is likely required since platelet-related events are pivotal in the pathophysiology of catastrophic stent thrombosis. Evidence for the importance of blockade of COX-1 and P2Y<sub>12</sub>—2 pivotal

pathways that amplify platelet activation—has been provided from the GEMINI-ACS-1 (Clinically significant bleeding with low-dose rivaroxaban versus aspirin, in addition to P2Y<sub>12</sub> inhibition, in acute coronary syndromes-1) trial which assessed the safety of replacing aspirin with rivaroxaban after PCI. In that trial, deletion of aspirin was associated with a greater number of stent thrombosis events that was observed early after PCI.<sup>13</sup> Therefore, it may be premature to dismiss the efficacy derived from DAPT in studies that were all undersized to adequately assess the effects of downgrading DAPT to antiplatelet monotherapy.

For long-term therapy, DT has been recommended with clopidogrel over aspirin.<sup>12</sup> However, the evidence for this recommendation is also lacking and poses a potential serious problem. It is well established that clopidogrel is associated with suboptimal platelet inhibition in 35% of patients due to genetic polymorphisms of cytochrome enzymes associated with clopidogrel metabolism and due to a high platelet reactivity phenotype arising from genetic and epigenetic factors. Patients with high platelet reactivity and patients with cytochrome P450 2C19 loss-of-function allele (*LoF*) are at significantly elevated risk for post-PCI thrombotic events.<sup>14,15</sup> With regard to that, the United States Food and Drug Administration mandated an assessment of *LoF* carrier status in clopidogrel-treated patients in a clinical trial as done in the recent GEMINI-ACS trial.<sup>13</sup> Therefore, the recommendation for treating patients with AF undergoing stenting particularly with clopidogrel as a single antiplatelet agent is a concern and should be further debated. The role of a stronger P2Y<sub>12</sub> inhibitor, ticagrelor (maybe at a lower dose) as a single antiplatelet agent in the presence of DOAC should be explored. Although DOACs are preferred over VKAs, the choice of a specific DOAC has not been established yet. At this time, it is prudent to follow the current treatment guidelines for patients with AF undergoing stenting.

## ARTICLE INFORMATION

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