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Triple antithrombotic therapy for patients with atrial fibrillation undergoing percutaneous coronary intervention☆

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ABSTRACT

Dual antiplatelet therapy (DAPT) has been the cornerstone of antithrombotic management for patients undergoing percutaneous coronary intervention (PCI). However, approximately 10% of these patients have concomitant atrial fibrillation (AF) and require chronic oral anticoagulant (OAC) in addition to DAPT. This traditional "triple therapy" has been associated with a three to four-fold increased risk of bleeding. The safety of non-vitamin K OAC (NOAC)-based strategies, using a NOAC plus a $P2Y_{12}$ inhibitor, has been compared to vitamin K antagonist (VKA)-based triple therapy in the PIONEER AF-PCI and REDUAL PCI randomized trials, both of which have demonstrated that NOAC-based strategies are safer and provide an attractive alternative to VKA-based triple therapy among AF patients who undergo PCI. This article reviews the rationale, evidence, and recent evaluation of triple antithrombotic therapy among AF patients undergoing PCI.

Contents

It has previously been demonstrated that, in stented patients, dual antiplatelet therapy (DAPT) is associated with a decreased risk of stent thrombosis and recurrent myocardial infarction (MI) as compared with either aspirin alone or the combination of vitamin K antagonist (VKA) plus aspirin.[1] Since then, DAPT with aspirin plus a $P2Y_{12}$ inhibitor has become a class I recommendation in American and European guidelines to prevent stent thrombosis, MI, cardiovascular (CV) death, and stroke among stented percutaneous coronary intervention (PCI) patients.[2,3] In contrast, among patients with atrial fibrillation (AF), anticoagulation using a VKA is superior to DAPT in reducing the risk of CV events.[4] Interestingly, approximately 10% of patients who undergo PCI also have concomitant AF, and a common practice has been to combine anticoagulant and DAPT (i.e. triple therapy) to simultaneously reduce the ischemic events associated with AF, as well as with the stent

Abbreviations and Acronyms: ACS, Acute Coronary Syndrome; AF, atrial fibrillation; BMS, bare metal stent; CV, cardiovascular; DAPT, dual antiplatelet therapy; DES, drug eluting stent; OAC, oral anticoagulant; MACE, major adverse cardiovascular event; MI, myocardial infarction; NOAC, non vitamin K oral anticoagulants; NVAF, non-valvular atrial fibrillation; PCI, percutaneous coronary intervention; VKA, vitamin K antagonist.

☆ Statement of Conflict of Interest: see page XX.

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placement.[5–7] Although this strategy has been supported by society guidelines, it has been associated with an unacceptable three to four-fold increase in the risk of bleeding complications.[8,9]

Non vitamin K oral anticoagulants (NOACs) offer a plausible alternative to VKAs. Compared with VKA, NOACs have a superior net clinical profile among patients with non-valvular AF (NVAF) and have become the standard of care for these patients.[10] Similarly, the efficacy of NOACs for the secondary prevention of atherothrombotic events has been demonstrated among patients in the post-ACS setting.[11] Among patients with AF who also undergo stenting, two randomized controlled trials, PIONEER AF-PCI and RE-DUAL PCI, have recently demonstrated that NOAC strategies are safer than VKA-based triple therapy.[12,13] These trials provide a strong basis to re-assess the common practice of using the traditional VKA-based triple therapy. This article reviews the background, rationale, evidence, and recent evaluation of the triple antithrombotic therapy.

The triple threat of VKA-based triple therapy

Historically, patients who required oral anticoagulant (OAC) were systematically excluded from randomized controlled trials (RCTs) evaluating the safety and efficacy of antiplatelet therapies following PCI. The evidence regarding the safety and efficacy of antithrombotic regimens for AF patients undergoing PCI was only supported by observational registries and post hoc analyses of RCTs evaluating either periprocedural anticoagulation or antiplatelet therapy among patients who finally required VKA during the study period.[6,14,15] Notably, these studies identified three major concerns associated with this regimen. First, VKA-based triple therapy was associated with an unacceptable increased risk of major bleeding, where the 'number needed to bleed' using triple therapy was as low as 13 patients when compared to aspirin alone.[9] Second, the reduction of the ischemic risk associated with VKA in these non-randomized studies was inconsistent, which may be in part due to the inherent flawed nature of these studies. For instance, the efficacy of VKA-based triple therapy as compared with DAPT based on historical observational data has widely ranged from a 2-fold decrease in the risk of major adverse cardiovascular events (MACE) to approximately 3-fold increase in the risk of stent thrombosis.[16,17] Third, only half of AF patients with a $CHADS_2$ ≥2 were treated with an anticoagulant following PCI,[6,14] which likely reflected the overall reluctance of physicians to start patients on a triple therapy antithrombotic regimen in the absence of robust evidence to support this strategy.

Finding the right dose of NOACs

Among patients with NVAF, four adequately powered RCTs enrolling >70,000 patients demonstrated that NOACs are non-inferior to VKA and are associated with a reduced rate of bleeding[18–21] Based on these results, NOACs have received a class I recommendation for stroke prevention in NVAF.[10] However, patients who required DAPT at baseline were excluded from these trials. Nevertheless, post-hoc analyses of these pivotal studies evaluated outcomes among subjects who were treated with antiplatelet therapy during the study period. Of interest, more than one third of AF patients randomized in the RELY trial (Randomized Evaluation of Long-Term Anticoagulation Therapy) for dabigatran were treated with either aspirin or clopidogrel during the study period.[22] As expected, the combination of full-dose OAC with an antiplatelet agent led to a significant increase in the overall risk of major bleeding without providing any additional efficacy. Bleeding risk increased significantly with the addition of a single antiplatelet (HR = 1.60, 95% CI (1.42–1.82)), and doubled when a DAPT regimen was added (HR = 2.31, 95% CI (1.79–2.98)). The relative risk of bleeding when either aspirin or clopidogrel was added to full-dose dabigatran was similar to that observed when these drugs were added to VKA. The use of antiplatelet therapy demonstrated no effect modification on either the primary efficacy or safety results (p-int = 0.73 and p-int = 0.79, respectively). These findings were consistent with the subsequent post-hoc analyses from the ARISTOTLE trial for apixaban (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) and the ENGAGE AF TIMI 48 trial for edoxaban (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation - Thrombolysis in Myocardial Infarction 48).[23,24] Similarly, there was no interaction between the use of aspirin and the treatment effect of either apixaban or edoxaban on the occurrence of stroke or systemic embolism and major bleeding. Finally, among AF patients enrolled in the ROCKET-AF trial (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation), 153 (1.1%) underwent PCI and had worse ischemic, as well as bleeding, outcomes as compared with those who did not undergo PCI in the trial. In this exploratory analysis, however, patients who underwent PCI and were receiving rivaroxaban had numerically lower rates of stroke and vascular death events as compared with VKA (stroke: 1/61 vs. 4/92 events; vascular death: 2/61 vs. 11/92 events), albeit at the expense of numerically increased rate of major bleeding (6/61) vs. (6/92 events).[25]

Due to the unacceptably high risk of bleeding when antiplatelet therapy was added to full-dose NOACs for patients undergoing PCI, the co-administration of low-doses of NOACs along with antiplatelet therapy has emerged as an attractive strategy to potentially reduce the risk of bleeding while preserving efficacy. In the post-ACS setting, NOAC-based triple therapy was evaluated in 7 randomized controlled trials.[11,26–31] Dose-finding phase II trials for dabigatran, apixaban, rivaroxaban, and darexaban on a background of standard of care DAPT post-ACS consistently demonstrated that the relationship between the NOAC dose and clinical benefit is in fact U-shaped.[26,29–31] Interestingly, there was a dose-dependent increase in major bleeding events at higher NOAC doses but without any improved efficacy when compared with the lower doses.[26,29] This became more evident when the NOACs were moved forward in the larger phase III trials, where the APPRAISE-2 trial for full-dose apixaban 5 mg twice-daily (i.e. dose for AF) post-ACS was terminated prematurely due to threefold increase in intracranial hemorrhage (0.1% for placebo vs. 0.3% for apixaban, HR = 4.06, 95% CI (1.15–14.38), p = 0.03) and fatal bleeding (0 in the placebo group vs. 5 fatal bleeds in the apixaban group) with no counterbalancing reduction in the rate of ischemic events (HR = 0.95, 95% CI = 0.80–1.11, p = 0.51).[28] In contrast, the ATLAS ACS 2-TIMI 51 phase III trial studied very low-dose rivaroxaban 2.5 and 5 mg twice-daily post-ACS, both of which are substantially lower than doses used in AF. Low-doses of rivaroxaban were associated with significant reduction in the rate of ischemic events (10.7% for placebo vs. 8.9% for combined rivaroxaban, HR = 0.84, 95% CI = 0.74–0.96, p = 0.008) without an increase in fatal bleeding or intracranial hemorrhage.[11,32]

To further reduce the risk of bleeding, rivaroxaban was also evaluated in addition to only a single antiplatelet therapy among patients immediately post-ACS in the GEMINI-ACS-1 trial, as well as among chronically stable CAD and PAD patients in the COMPASS trial.[33,34] In the GEMINI-ACS-1 trial, patients were randomized within 10 days of an ACS event to either standard of care $P2Y_{12}$ inhibitor plus either aspirin or very-low-dose rivaroxaban 2.5 mg BID (dual-pathway combination used in ATLAS ACS 2-TIMI 51).[33] The dual pathway combination with rivaroxaban plus $P2Y_{12}$ inhibitor was non-inferior to standard of care DAPT and was associated with a similar risk of clinically significant bleeding as standard of care DAPT (5% vs. 5%, HR = 1.09, 95% CI = 0.80–1.50, p = 0.58). While GEMINI-ACS-1 randomized patients immediately post-ACS, COMPASS trial randomized patients with stable atherosclerotic vascular disease to receive either standard of care aspirin 100 mg monotherapy vs. very-low-dose rivaroxaban 2.5 mg twice-daily plus aspirin 100 mg daily vs. low-dose rivaroxaban 5 mg twice-daily (N = 27,395). Interestingly, COMPASS was stopped early after a mean follow-up of 23 months due to overwhelming efficacy in the very-low-dose rivaroxaban 2.5 mg twice-daily plus aspirin group, where the combination regimen was associated with a significant reduction

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