REVIEW ARTICLE

Antithrombotic therapy in patients with atrial fibrillation and coronary artery disease

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ABSTRACT

Atrial fibrillation and coronary artery disease are commonly coexisting conditions that necessitate the use of an oral anticoagulant as well as dual antiplatelet therapy. Commonly referred to as triple oral antithrombotic therapy (TT), this helps prevent ischemic stroke and myocardial infarction but comes at the expense of an increased risk of bleeding. There is a growing body of evidence that the omission of aspirin from TT has the same preventive efficacy in terms of major adverse cardiacvascular and cerebrovascular events (MACCE) with significantly lower bleeding events. The combination of antiplatelet agents and direct oral anticoagulants (DOAC) is a matter of ongoing research. However, initial studies showed favorable safety profile of DOAC over vitamin K antagonist in combination with antiplatelet agents.

Key words: Atrial fibrillation, cad, dual antiplatelet therapy, triple antithrombotic therapy

INTRODUCTION

Coronary artery disease (CAD) occurs in 20%–30% of patients with atrial fibrillation (AF), and 5.3%–28% of hospitalized patients with acute coronary syndrome (ACS) develop new-onset AF during their hospitalization.[1-4] In addition, 5% of patients undergoing percutaneous coronary artery intervention (PCI) and stent placement require long-term anticoagulation because of AF.[5,6] Patients with AF with a CHA2DS2-VASc score of two or more and ACS have indications for oral anticoagulation and dual antiplatelet therapy (DT) with aspirin and a P2Y12 receptor inhibitor. The concurrent use of all three agents, termed triple oral antithrombotic therapy (TT), significantly increases the risk of bleeding.[7,8]

Currently, oral anticoagulation is the standard of care for AF patients who have a score of two or greater in men and three or greater in women on CHA2DS2-VASc score to reduce the thromboembolic risk. According to the American Heart Association guidelines, anticoagulation options are warfarin, dabigatran, rivaroxaban, apixaban, or edoxaban.[9,10] According to American College of Cardiology/American Heart Association, patients with ACS should be started on aspirin and P2Y12 inhibitors whether they are a candidate for PCI or not.[11-13] Given the aging population and increasing prevalence of risk factors for both CAD and the development of AF with age, at some point a large number of patients with AF and ACS may require triple oral antithrombotic therapy.

DT VS. OAC FOR STROKE PREVENTION IN AF PATIENTS

DT for one year is the standard of care for all patients with ACS whether the patient has undergone stent placement or is being treated medically. The Effect of Clopidogrel in addition to Aspirin in patients with acute coronary syndrome without ST-segment elevation study showed 20% reduction in the composite of cardiovascular mortality,

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myocardial infarction, and stroke in ACS patients who received aspirin and clopidogrel for 12 months vs. aspirin alone. In addition, subgroup analysis showed consistent results whether the patient had revascularization or not.[11]

The question arose as to whether DT was sufficient to prevent stroke in patients with concomitant AF without need for additional oral anticoagulant. Long-term efficacy of DT compared with vitamin K antagonist for stroke prevention was addressed in a prospective study that terminated early because of significantly higher thromboembolic events in the DT group. The results revealed an annual risk of stroke in OAC vs. DT of 3.93% vs. 5.60%; with a relative risk of 1.44 (1.18–1.76; $P = 0.0003$).[14] Another meta-analysis showed similar results with a minor increase in extracranial hemorrhage in the OAC group by 0.3%.[15]. Moreover, warfarin is superior to DT in reducing plasma thrombogensis marker levels in patients with AF.[16] Thus, both the United States and European guidelines do not recommend any antiplatelet therapy as a prophylaxis for stroke in patients with AF.[9,17,18]

Adding an oral anticoagulant to DT comes with the risk of higher bleeding rates when compared to two antithrombotic agents. In the WOEST trial that compared warfarin plus clopidogrel vs. triple therapy, the latter group had a higher risk of bleeding (44.4% vs. 19.4; hazard ratio [HR], 0.36; 95% confidence interval [CI], 0.26–0.40;$P < 0.001$).[7] Khurram *et al.* found that in patients requiring anticoagulation therapy with warfarin, the addition of DT was associated with a 6.6% major bleeding risk. Rogacka *et al.*[19] found a 4.7% incidence of major bleeding complications during the triple therapy. Bleeding commonly occurred within the first month of triple therapy in the majority of patients.[20,21]

Duration of TT and risk of bleeding

The absence of a major bleeding event in the first 30 days of TT does not necessarily predict outcomes up to the end of the first year of TT. Indeed, a meta-analysis that included patients with AF and CAD on TT showed that the risk of major bleeding increased by almost six-fold by the end of 12 months' therapy (12%) compared with the first 30 day of TT (2.2%).[22] Moreover, the RE-LY study that compared efficacy and safety of dabigatran compared with warfarin in patients with AF showed that intracranial hemorrhage in anticoagulated patients correlates with concurrent antiplatelet therapy which was found to be the most important modifiable independent risk factor for intracranial hemorrhage (HR, 2.9, $P < 0.001$).[23]

If shorter courses of TT decrease the risk of major bleeding, would the shorter duration of TT compromise efficacy? The ISAR-TRIPLE trial was an open-label study that addressed the efficacy of TT based on the duration of TT. All patients in the trial received aspirin and OAC and were then randomized to six weeks of clopidogrel therapy vs. six months of clopidogrel. The primary end point was major adverse cardiovascular and cerebrovascular events (MACCE) at nine months. The results did not show a significant difference in the primary endpoint; a longer TT duration was not superior to shorter TT in terms of preventing thromboembolic events.[24]

VKA and antiplatelet therapy: How to mitigate the risk of bleeding?

Konishi *et al.*[25] found that in patients with AF who had PCI on TT with a therapeutic INR between 1.6 and 2.6 and a median time in the therapeutic range of 78.4%, TT therapy was not associated with MACCE ($P = 0.89$) nor major bleeding ($P = 0.80$) as compared with DT. The conclusion was that a slightly lower and a tightly controlled INR may be the answer for safer TT without compromising efficacy.

The WOEST trial is a landmark study that addressed safety of TT as a primary end point (bleeding events) and efficacy in preventing thrombotic events as a secondary point in terms of cardiac ischemic events, stroke, and stent thrombosis. Patients with AF and CAD were randomized before coronary angiography to TT (warfarin, aspirin, clopidogrel) or DT (warfarin and clopidogrel). TT associated with a significantly higher number of bleeding events. Ironically, the results showed better efficacy with DT. The composite of secondary endpoints (death, MI, stent thrombosis, strokes) was significantly lower in DT (11.3% vs. 17.7% $P = 0.025$ HR, 0.60, (0.38–0.94).[7]

DOAC as an alternative to VKA?

This raises the question if DOACs will be a safer alternative to warfarin in TT by avoiding variation in levels of anti-coagulation. Rivaroxaban was the first DOAC that had positive outcome as an add-on to DT in patients with AF and CAD after PCI. PIONEER AF-PCI trial examined the safety and efficacy of rivaroxaban 15 mg daily in addition to P2Y12 (group 1), vs. rivaroxaban 2.5 mg daily as a part TT (group 2), and vs. VKA plus DT (group 3) for 1, 6, or 12 months. Clinically significant bleeding was lower in the two groups receiving rivaroxaban than in the group receiving standard therapy (16.8% in group 1, 18.0% in group 2, and 26.7% in group 3; HR for group 1 vs. group 3, 0.59; 95% CI, 0.47–0.76; $P < 0.001$; HR for group 2 vs. group 3, 0.63; 95% CI, 0.50–0.80; $P < 0.001$). In addition, there was no significant difference in thrombotic events (MACCE) among the three groups.[26] However, rivaroxaban doses used in PIONEER AF_PCI trial are lower than stroke preventive dose used in

ROCKET AF trial.[27] Therefore, the results of PIONEER trial should be taken with caution. Longer follow-up period and bigger study population are needed to ascertain the safety of such an approach.

In the same patient population, similar results were found when dabigatran and P2Y12 (clopidogrel or ticagrelor) based DT was compared with TT (warfarin, Aspirin and P2Y12 inhibitor). RE-DUAL PCI trial has shown superiority of dabigatran-based DT compared with TT at 110 mg dose (included elderly >80 year old) in terms of bleeding events (15.4% vs. 26.9% (HR, 0.52; 95% CI, 0.42–0.63; $P < 0.001$ for noninferiority; $P < 0.001$ for superiority). With non-inferiority for dabigatran 150 mg dose 20.2% for DT vs. 25.7% for TT (HR, 0.72; 95% CI, 0.58–0.88; $P < 0.001$ for noninferiority). No significant difference in thromboembolic events was found between the two groups. Nevertheless, higher number of stent thrombosis in dabigatran 110-mg arm was found but it did not reach statistical significance.[28]

Apixaban is no exception. In AUGUSTUS trial, 4614 patients with AF and CAD were randomized to apixaban 5 mg twice daily or vitamin K antagonist in addition to P2Y12 in open-label part of the study. Then the patients were randomized to aspirin or placebo. Unsurprisingly, patients received apixaban and P2Y12 without aspirin had the lowest bleeding events without significant difference in mortality and ischemic events among the groups. In general, apixaban group has one-third reduction in bleeding events as compared with vitamin K antagonist-based antithrombotic regimen 10.5% vs. 14.7% (HR, 0.69; 95% CI, 0.58–0.81; $P < 0.001$ for both noninferiority and superiority).[29]

Furthermore, two recent meta-analysis addressed safety and efficacy of DT (an oral anticoagulant plus P2Y12 inhibitor) vs. conventional TT (warfarin, aspirin, and P2Y12) have shown reduction in minor and major bleeding events by half in DT compared with TT without significant difference in all-cause mortality, major adverse cardiac events, thromboembolic events, myocardial infarction, and stent thrombosis.[30,31]

DOACs in combination with DT in patient with CAD without AF

The use of DOACs in combination with aspirin and clopidogrel was studied in patients with ACS without AF [Table 1]. In the Re-DEEM study, adding different doses of dabigatran to DT vs. placebo was associated with significant increases in the risk of bleeding by 77% with the lowest dose, and up to four-fold risk with the higher doses of dabigatran without any additional benefit; for 50 mg (HR, 1.77; 95% CI, 0.70–4.50); for 75 mg (HR, 2.17; 95% CI, 0.88–5.31); for 110 mg (HR, 3.92; 95% CI, 1.72–8.95); and for 150 mg (HR, 4.27; 95% CI, 1.86–9.81).[32] Apixaban plus DT vs. placebo plus DT also had disappointing results and led to the early termination of the APPRAISE trial because of unacceptable rates of total bleeding.[33]

Ticagrelor and prasugrel as a part of TT

Data are scarce when it comes to other P2Y12 inhibitors as a part of TT. A Swedish study compared the safety and efficacy of TT (aspirin, clopidogrel, and warfarin) vs. DT (ticagrelor and warfarin) in patients with AF and CAD after stenting for only three months retrospectively. The results did not show significant differences between the two groups in terms of bleeding and thrombo-embolic events.[34] In Re-Dual PCI trial, subgroup analysis showed a 15%–50% increase in bleeding event rate in patients who had taken ticagrelor as part of TT with VKA or DT with dabigatran vs. other P12Y2 inhibitors.[28] Similar results were observed in AUGUSTUS trial where higher bleeding rate was found in patients who had received prasugrel and ticagrelor vs. clopidogrel.[29] The results of the ongoing prospective MANJUSRI trial are eagerly anticipated––which would provide data on the better combination therapy (ticagrelor and warfarin vs. aspirin, clopidogrel, and warfarin) for patients with AF and CAD.[35]

Guidelines

According to the American Heart Association guidelines for AF that were published in 2014 and an update in 2019, it may be reasonable to use clopidogrel in combination with oral anticoagulants (without specifying a particular anticoagulant) without aspirin after coronary revascularization.[9,17] On the contrary, the ESC 2016 guidelines adopted a shorter period of TT of a month followed by dual therapy (OAC plus a single antiplatelet).[18]

CONCLUSION

In patients with AF undergoing PCI, it may be reasonable to use rivaroxaban, dabigatran, or apixaban in combination with clopidogrel without aspirin. Such combination does mitigate the risk of bleeding without compromising efficacy in terms of ischemic events and mortality. Rivaroxaban, dabigatran, and apixaban are safer as part of triple/dual therapy when compared with VKA without compromising efficacy. There is a growing body of evidence that combination of an oral anticoagulant (rivaroxaban, dabigatran, and apixaban or VKA) and P2Y12 platelet inhibitors without aspirin is as effective as TT and it carries less risk of bleeding, which would the approach of choice for high bleeding risk patients who have AF undergoing PCI. In addition, use of clopidogrel instead of ticagrelor or prasugrel as a part of DT or TT in

Table 1: Trials that studied the efficacy and safety of adding oral anticoagulant (VKA or NOAC) on DAPT

Study	Design	Outcome	Follow up	Population	Comparison	Bleeding endpoint	Ischemic endpoint
Mega *et al*, 2009 (32)	Randomised, double blind, phase II	Saftey endpoint:TIMI bleeding (major or minor) or requiring medical attention), efficany end point: Death, MI, stroke	6 months	3491 patients after ACS	ASA only or ASA plus thienopyridine, randomized to receive placebo or Rivaroxiban 5-20mg	significant bleeding with rivaroxaban versus placebo increased in a dose-dependent manner (hazard ratios [HRs] 2.21 [95% CI 1.25-3.91] for 5 mg, 3.35 [2.31-4.87] for 10 mg, 3.60 [2.32-5.58] for 15 mg, and 5.06 [3.45-7.42] for 20 mg doses; p<0.0001	primary efficacy endpoint were 5.6% (126/2331) for rivaroxaban versus 7.0% (79/1160) for placebo (HR 0.79 [0.60-1.05], p=0.10)
APPRAISE Steering Committee and investigators *et al*, 2009	Double blinded, placebo controlled, phase II	Primary outcome: Major or non-Major bleeding, seconday outcome: cardiovascular death, myocardial infarction, severe recurrent ischemia, or ischemic stroke	6 months	1715 patients with STEMI and STEMI and 1 additional risk factor for ischemic event	Nearly all received ASA and 76% received Plavix, patient randmoized to different doses of Apixaban or placebo	10mg BID and 20mg daily were terminated early due to excess total bleed. Compared with placebo, apixaban 2.5 mg twice daily (hazard ratio, 1.78; 95% confidence interval, 0.91 to 3.48; P=0.09) and 10 mg once daily (hazard ratio, 2.45; 95% confidence interval, 1.31 to 4.61; P=0.005)	Apixiban resulted in lower rates of secondary end point. However, ithe ncrease in bleeding was more pronounced and the reduction in ischemic events.
oldgren *et al*, 2011	Randomized, double-blind, phase II trial	Primary outcome was major or minor bleeding, secondary outcome was reduction in D-Dimer levels or CVD ischemic events	Up to 28 weeks	1861 patient with NSTEMI and STEMI with one major risk factors for CVD	DAPT with different strength of Dabigatran or placebo	bleeding: Dose-dependent increase with dabigatran, hazard ratio (HR) 1.77 (95% confidence intervals 0.70, 4.50)	Fourteen (3.8%) patients died, had a myocardial infarction or stroke in the placebo group compared with 17 (4.6%) in 50 mg, 18 (4.9%) in 75 mg, 12 (3.0%) in 110 mg, and 12 (3.5%) in the 150 mg dabigatran groups
Dewilde *et al*, 2013	Open-Label, randomizes, controlled trial	Primary safety endpoint: Bleed within 1 year, secondary endpoint of death, myocardial infarction, stroke, target-vessel revascularisation	12 months	573 patients receiving anti-coagulation and undergoing PCU	Anti-coagulation plus plavis (double therapy) or plus ASA and Plavix (triple therapy)	Bleeding episodes were seen in 54 (19·4%) patients receiving double therapy and in 126 (44·4%) receiving triple therapy (hazard ratio [HR] 0·36, 95% CI 0·26-0·50, p<0·0001)	31 (11·1%) patients in the double-therapy group and in 50 (17·6%) in the triple-therapy group After correction for imbalance in baseline characteristics, the HR remained similar (0·56, 95% CI 0·35–0·91).
Gibson *et al*, 2016	Randomized, controlled, open label	Primary safety outcome was clinically significant bleeding, secondary end point	1,6, 12 months	2124 patients with Non-valular atrial fibrillation undergoing PCI	Low dose rivaroxiban + thienopyridine (group1), Low dose rivaroxiban+ + DAPT (group2), Warfarin with INR 2-3 + DAPT	Bleeding(16.8% in group 1, 18.0% in group 2, and 26.7% in group 3; hazard ratio for group 1 vs. group 3, 0.59; 95% confidence interval [CI], 0.47 to 0.76; P<0.001; hazard ratio for group 2 vs. group 3, 0.63; 95% CI, 0.50 to 0.80; P<0.001)	Death from cardiovascular causes, myocardial infarction, or stroke were similar in the three groups (Kaplan–Meier estimates, 6.5% in group 1, 5.6% in group 2, and 6.0% in group 3; P values for all comparisons were nonsignificant).
Lopres *et al*, 2019	Randomized, controlled, open label	Primary outcome: major and clinically relevant non major bleeding. Secondary outcome: composite of death and hospitalization and composite of death and ischemic events	7 months	4614 patients with atrial fibrillation and coronary artery disease	Apixaban+ P2Y12 +/- Aspirin Vs VKA +P2Y12 +/- Aspirin	Bleeding events 10.5% in apixaban group vs 14.7% in VKA group (HR 0.69, 95% CI 0.58 to 0.81 P <0.001)	Death or hospitalization 23.5% in apixaban group vs 27.4% in VKA group (HR 0.83, 95%CI 0.770 to 0.93, P=0.002) Similar incidence of ischemic event

patients at high risk of bleeding is associated with lower bleeding event.

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Conflicts of interest
There are no conflicts of interest.

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