Published in final edited form as:

Curr Cardiol Rep. ; 20(11): 110. doi:10.1007/s11886-018-1045-0.

Management of Anticoagulation in Patients with Atrial Fibrillation Undergoing PCI: Double or Triple Therapy?

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Abstract

Purpose of review: This review aims to discuss the use of antithrombotic therapy in patients with atrial fibrillation who undergo coronary stenting with emphasis on the use of double vs triple therapy.

Recent findings: When combined with systemic anticoagulation, dual antiplatelet therapy results in an unacceptable increase in bleeding without any improvement in prevention of thrombotic events. Direct oral anticoagulants combined with single antiplatelet therapy have reduced bleeding compared with warfarin plus dual antiplatelet therapy. Triple anticoagulation therapy with warfarin or direct oral anticoagulants leads to an excess of bleeding and is not superior in preventing thrombotic events.

Summary: Recent randomized, controlled trials have shown a significant reduction in major bleeding events in patients treated with dual antithrombotic therapy compared with triple therapy

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Conflict of Interest

Dr. Benjamin E. Peterson declares that he has no conflict of interest.

Dr. Deepak L. Bhatt discloses the following relationships:

Advisory Board: Cardax, Elsevier (Practice Update Cardiology), Medscape Cardiology, Regado Biosciences. Board of Directors: Boston VA Research Institute, Society of Cardiovascular Patient Care, TobeSoft.

Chair: American Heart Association Quality Oversight Committee. Data Monitoring Committees: Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St. Jude Medical, now Abbott), Cleveland Clinic, Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ENVISAGE trial, funded by Daiichi Sankyo), Population Health Research Institute.

Honoraria: American College of Cardiology (Senior Associate Editor, Clinical Trials and News, [ACC.org](https://www.acc.org); Vice-Chair, ACC Accreditation Committee), Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; RE-DUAL PCI clinical trial steering committee funded by Boehringer Ingelheim), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees), HMP Global (Editor in Chief, Journal of Invasive Cardiology), Journal of the American College of Cardiology (Guest Editor; Associate Editor), Population Health Research Institute (for the COMPASS operations committee, publications committee, steering committee, and USA national co-leader, funded by Bayer), Slack Publications (Chief Medical Editor, Cardiology Today's Intervention), Society of Cardiovascular Patient Care (Secretary/Treasurer), WebMD (CME steering committees).

Other: Clinical Cardiology (Deputy Editor), NCDR-ACTION Registry Steering Committee (Chair), VA CART Research and Publications Committee (Chair).

Research Funding: Abbott, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Chiesi, Eisai, Ethicon, Forest Laboratories, Idorsia, Ironwood, Ischemix, Lilly, Medtronic, PhaseBio, Pfizer, Regeneron, Roche, Sanofi Aventis, Synaptic, The Medicines Company.

Royalties: Elsevier (Editor, Cardiovascular Intervention: A Companion to Braunwald's Heart Disease); Site Co-Investigator: Biotronik, Boston Scientific, St. Jude Medical (now Abbott), Svelte; Trustee: American College of Cardiology; Unfunded Research: FlowCo, Merck, PLX Pharma, Takeda.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

without any difference in efficacy. These findings call into question whether triple therapy should remain a part of standard practice.

Keywords

Atrial Fibrillation; Percutaneous Coronary Intervention; Antiplatelet Therapy; Anticoagulation

Introduction

Atrial fibrillation affects approximately thirty-three million patients worldwide, about 30% of whom have coronary artery disease and 5-10% of whom will undergo percutaneous coronary intervention (PCI) during their lifetimes [1, 2, 3]. Systemic anticoagulation has been shown to reduce the incidence of stroke in patients with atrial fibrillation by approximately 60% and has been shown to be superior to dual antiplatelet therapy (DAPT) in this regard [4, 5]. Yet, patients with atrial fibrillation are often under-treated for stroke prevention. Though patients with AF have nearly double the mortality risk of the population, in a global registry, only 53% of all patients with AF were treated with anticoagulation for stroke prevention [6,7].

However, for patients undergoing coronary stenting, DAPT has been shown to be superior to oral anticoagulation with warfarin at preventing death, myocardial infarction, and stent thrombosis [8, 9]. This led to the development of “triple therapy” (systemic anticoagulation with warfarin plus clopidogrel and aspirin) as the standard of care in preventing stroke as well as Major adverse cardiovascular events (MACE) in patients with atrial fibrillation who undergo coronary stenting.

In an era of newer generation stenting with significantly lower rates of stent thrombosis, the importance of triple therapy has been called into question. In the “What is the Optimal antiplatelet and anticoagulant therapy in patients with oral anticoagulation and coronary StenTing” (WOEST) trial, 573 patients with atrial fibrillation on warfarin who underwent PCI were randomized to receive traditional triple therapy or double therapy with warfarin plus clopidogrel. As expected, there was a dramatic reduction in major bleeding between double and triple therapy (19.4% vs 44.4%; NNT=4 to prevent one major bleeding episode), but there was actually a decrease in the combined endpoint of death, myocardial infarction, revascularization, stroke, or stent thrombosis as well (11.1% vs 17.6%) [10]. It is important to note that all patients received aspirin while in the hospital, including those discharged on therapeutic warfarin and clopidogrel. Please see table 1 for a summary of data from key trials discussed in this review.

In contrast to WOEST, in the ISAR-TRIPLE (Triple Therapy in Patients on Oral Anticoagulation After Drug Eluting Stent Implantation) trial, 614 patients with atrial fibrillation who underwent PCI were randomized to receive six weeks or six months of triple therapy. In this study, there was no significant difference in bleeding or MACE between the two groups [11]. In both WOEST and ISAR-TRIPLE, there was a significant up-front risk of bleeding with triple therapy, and most bleeding occurred in the first 4-6 weeks of therapy. This calls into question the recent common practice of using triple therapy for a brief duration, such as 30 days.

Updated practice guidelines in the US and Europe have recommended shorter durations of triple therapy with oral anticoagulation and dual antiplatelet therapy but have not yet gone so far as to recommend going directly to oral anticoagulation and single antiplatelet therapy as in WOEST [10, 12, 13, 14]. Despite these recommendations, it has been shown in a nationwide registry that only 27.7% of all patients with atrial fibrillation who undergo PCI are treated with triple therapy [15]. Undoubtedly, this is related to adherence, competing bleeding risk and complications, cost and many other patient or physician factors. Regardless of these, the question of what should be done in the situation of a patient with AF who undergoes PCI remains important in an era of improving stent technology, use of direct oral anticoagulants, which have significantly better bleeding profiles when compared with warfarin, and a recent wealth of clinical trial data.

Bleeding risk and Thrombosis Risk

There is significant overlap among the factors that predispose to bleeding risk and thrombotic events: age, prior bleeding, sex, prior thrombotic events, chronic kidney disease (CKD), anemia, and non-steroidal anti-inflammatory drugs (NSAID) use independently predict bleeding [16, 17]. To one degree or another, these are known to be independent predictors of ischemic events as well. In a large nationwide registry, major bleeding events accounted for approximately 12% of all PCI-related deaths and a significant increase of in-hospital mortality [18]. It has also been shown that bleeding episodes lead to interruption or discontinuation of appropriate antithrombotic therapy and subsequent thrombotic events [19]. “Nuisance bleeding,” on the other hand, which is common in all forms of oral anticoagulation, was not associated with major bleeding, stroke, or systemic embolism at six months or discontinuation of anticoagulation therapy in a large nationwide registry [20].

There is also significant overlap in the risk factors that predispose to stroke and myocardial ischemic events, and undoubtedly similar pathogenesis with respect to platelet activation and inflammation [21]. The 902 patients with prior stroke enrolled in the APPRAISE-2 (Apixaban for Prevention of Acute Ischemic Events 2) trial, a prospective clinical trial studying the use of DOACs to prevent MACE after ACS, had significantly higher rates of death, myocardial infarction, and recurrent stroke [22]. The patients who benefit most from oral anticoagulation are the same patients who benefit most from antiplatelet therapy because of the thrombogenic nature of atrial fibrillation.

The relative frequency and severity of bleeding and thrombosis events are often not well appreciated. This is true for patients on anticoagulation with or without antiplatelet therapy: For example, patients randomized to rivaroxaban for primary stroke prevention in ROCKET-AF had a 14.9% annual rate of major and clinically relevant minor bleeding, and only a 2.2% annual rate of stroke or systemic embolism [23]. Patients with AF undergoing PCI randomized to warfarin triple therapy in WOEST suffered a 44.4% annual risk of major or minor bleeding vs a 17.6% annual rate of death, myocardial infarction, revascularization, stroke, or stent thrombosis [10]. The differential frequency of bleeding vs MACE events may continue to become sharper as newer generation stents continue to be adopted worldwide and the use of bare metal stents declines [24].

Furthermore, the relative bleeding risk of different antithrombotic therapies is often not appreciated. For example, in AVERROES (Apixaban Versus Acetylsalicylic Acid [ASA] to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment), in 5599 patients with atrial fibrillation who were unable to take warfarin and randomized to aspirin vs apixaban, there was a similar rate of bleeding among patients taking aspirin compared with patients taking full-dose apixaban [25]. Clopidogrel, on the other hand, has been shown to cause more potent platelet inhibition, but less bleeding, than 325 milligrams of aspirin [26]. In a follow-up analysis of the randomized, blinded, trial of clopidogrel versus aspirin in patients at risk of ischemic events (CAPRIE) trial, patients taking clopidogrel had less hospitalization for gastrointestinal bleeding than patients taking full-dose aspirin [27]. Aspirin may be over-the-counter and very commonly taken, but its use is associated with important bleeding risk.

Direct Oral Anticoagulants

In recent years, the advent of direct oral anticoagulants (DOACs) such as dabigatran, rivaroxaban, apixaban, and edoxaban has significantly changed the landscape of anticoagulation to prevent stroke in patients with atrial fibrillation. In clinical trials these direct oral anticoagulants were shown to be non-inferior to warfarin in preventing stroke and systemic embolism and superior to warfarin in causing less major bleeding [23, 28, 29, 30]. Dabigatran 150 mg twice daily was shown to be superior to warfarin with regard to preventing stroke and systemic embolism and similar with regard to bleeding episodes, whereas dabigatran 110 mg twice daily was similar to warfarin with regard to preventing stroke and systemic embolism but superior with regard to bleeding [28]. Apixaban caused significantly less fatal bleeding, intracranial bleeding and gastrointestinal bleeding than warfarin; the 30-day case fatality rate of a bleeding episode on apixaban was significantly lower than a bleeding episode on warfarin, even without any available reversal agents at the time [29, 31, 32, 33]. Moreover, apixaban was superior to warfarin in preventing stroke or systemic embolism and all-cause mortality [29]. Data for rivaroxaban and edoxaban also compare favorably against warfarin [23, 30]. Increasingly, these DOACs are becoming the standard of care. Undoubtedly, as specific reversal agents become more widely available, clinical comfort level with the DOACs will continue to increase [34, 35].

Other specific frontiers in the use of DOACs continue to emerge as experience and trial data come to light [36]. For example, it has been shown that patients over age 80 (who are at significantly increased risk for both bleeding and stroke) had less bleeding on apixaban and a trend towards less stroke than patients on warfarin [37, 38]. Patients with renal disease are also at significantly increased risk of both stroke and bleeding—and the patients with lower GFRs had the greatest relative benefit to taking DOACs vs warfarin with respect to bleeding, as well as stroke or systemic embolism [39, 40, 41, 42]. Patients with end-stage renal disease (ESRD) are among the highest risk for bleeding and stroke [43]. RENAL-AF (Trial to Evaluate Anticoagulation Therapy in Hemodialysis Patients With Atrial Fibrillation), an ongoing clinical trial in which patients with ESRD and atrial fibrillation are randomized to apixaban vs warfarin, may show both safety and efficacy in this important subgroup of patients [[clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02942407) ID NCT02942407]. While the label for DOACs in the US includes patients with “non-valvular AF,” the reality is that clinical trials have included

patients with varying degrees of aortic stenosis, mitral regurgitation, bioprosthetic valves, and others; these patients have shown a consistent benefit from taking DOAC vs warfarin [44]. However, patients with mechanical valves should not receive DOACs unless further adequately powered studies are performed. The Randomized, Phase II Study to Evaluate the Safety and Pharmacokinetics of Oral Dabigatran Etexilate in Patients after Heart Valve Replacement (RE-ALIGN), was terminated early because of increased thromboembolic and bleeding events in patients with mechanical heart valves randomized to dabigatran, though some small studies are still underway [45, [ClinicalTrials.gov](#) Identifiers: [NCT03566303](#), [NCT02894307](#)].

Prior to the more recent clinical trials directly studying the use of DOAC and antiplatelet therapies in patients with AF who undergo PCI, there were a number of other trials looking at the safety and efficacy of DOACs in treating patients with ACS. In “Rivaroxaban Versus Placebo in Patients with Acute Coronary Syndromes (ATLAS ACS-TIMI 46), rivaroxaban 5-20 mg vs placebo was added to standard therapy in 3491 patients with ACS, causing a dose-dependent increase in bleeding [46]. Later, in ATLAS ACS-TIMI 51, 15,526 patients with ACS randomized to low-dose rivaroxaban or placebo, the addition of rivaroxaban 2.5 mg to standard therapy after PCI in patients without atrial fibrillation significantly reduced the combination of death, MI, or stroke but also significantly increased the risk of major bleeding [47]. Apixaban for Prevention of Acute Ischemic Events 2 (APPRAISE 2), a randomized controlled trial of 7392 patients with ACS treated with full-dose apixaban vs placebo plus standard therapy, was terminated early due to increased bleeding, but also a lack of reduction in ischemic events [48]. Even in these patients with high ischemic risk, and using apixaban rather than warfarin, there was no net clinical benefit to taking full-dose triple therapy. Interestingly, in APPRAISE 2, the use of aspirin plus a DOAC significantly increased bleeding regardless of clopidogrel use [49].

In a meta-analysis of ACS trials comparing DOAC use in combination with single and dual antiplatelet therapy, it was shown that double therapy with DOAC and single antiplatelet therapy was associated with significantly less major bleeding and similar rates of ischemic events when compared with the use of a DOAC with DAPT [50]. This lack of improvement in ischemic events with dual vs single antiplatelet therapy in the presence of a DOAC has been somewhat puzzling, given that it has been clearly shown that DAPT is superior to aspirin or P2Y₁₂ inhibition alone at preventing MACE events in high risk patients [8-9]. It has been postulated that the DOACs themselves may possess some intrinsic antiplatelet effects [51].

Recent Clinical Trials

In the PIONEER-AF PCI trial (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) 2124 patients with atrial fibrillation undergoing PCI were randomized to receive rivaroxaban 15 mg daily plus clopidogrel vs rivaroxaban 2.5 mg daily plus aspirin and clopidogrel vs triple therapy with warfarin, clopidogrel, and aspirin [52]. Dual antiplatelet therapy was continued for 1, 6, or 12 months depending on the choice

of the investigators. The rates of clinically evident bleeding were 16.8% for rivaroxaban 15 mg plus single antiplatelet therapy, 18% for rivaroxaban 2.5 plus dual antiplatelet therapy, and 26.7% in the warfarin triple therapy group ($p<0.001$ for both). Efficacy endpoints were not different between the three groups [53].

A post hoc analysis of PIONEER AF showed that among the three groups there was a significant reduction in the rate of death or recurrent hospitalization among patients who received the two rivaroxaban doses vs warfarin (34.9% for rivaroxaban 15 mg plus single antiplatelet therapy (SAPT) and 31.9% for rivaroxaban 2.5 mg plus DAPT vs 41.9% for warfarin triple therapy) [54]. Though this trial was not powered for efficacy, this combined endpoint is likely to be clinically meaningful and signals a net clinical benefit beyond bleeding reduction [55]. Both an ATLAS-like regimen of DAPT plus very low-dose rivaroxaban and a WOEST-like regimen of oral anticoagulation plus SAPT significantly reduced bleeding events without compromising efficacy.

The RE-DUAL PCI trial (Randomized Evaluation of Dual Antithrombotic Therapy with Dabigatran versus Triple Therapy with Warfarin in Patients with Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention) included 2725 patients with atrial fibrillation undergoing PCI, randomized to receive triple therapy with warfarin, aspirin, and clopidogrel or double therapy with dabigatran 110 mg or 150 mg and clopidogrel (or ticagrelor). Older patients outside the US were excluded from the dabigatran 150 mg group [56]. The primary endpoint of International Society on Thrombosis and Hemorrhage (ISTH) major or clinically relevant minor bleeding occurred in 15.4% of patients in the dabigatran 110 mg group vs 26.9% of patients receiving warfarin triple therapy; and it occurred in 20.2% of patients taking dabigatran 150 mg group vs 25.7% of patients in the corresponding warfarin triple therapy group ($p<0.001$ for superiority). Of special note, the patients on warfarin triple therapy discontinued aspirin after 90 days if they received a drug eluting stent and 30 days if they received a bare metal stent—and yet the significant excess of bleeding with triple therapy persisted. There was no difference in efficacy among these groups ($p=0.005$ for noninferiority) [47].

A meta-analysis that included the WOEST, ISAR-TRIPLE, PIONEER-AF PCI, and RE-DUAL PCI trials recently showed that patients with atrial fibrillation undergoing PCI who received dual antithrombotic therapy had 47% less TIMI major or minor bleeding than patients receiving triple therapy. This pooled analysis also did not detect a difference in trial-defined MACE events or individual outcomes of death, cardiovascular death, myocardial infarction, stent thrombosis, or stroke between patients taking oral anticoagulants plus single antiplatelet therapy vs double therapy [58].

ENTRUST-AF PCI (Edoxaban Treatment Versus Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention) is an ongoing trial with similar design to RE-DUAL PCI, comparing low and high dose edoxaban with warfarin triple therapy [59], [clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02866175) ID [NCT02866175](https://clinicaltrials.gov/ct2/show/study/NCT02866175)]. AUGUSTUS (An Open-label, 2×2 Factorial, Randomized Controlled, Clinical Trial to Evaluate the Safety of Apixaban vs. Vitamin K Antagonist and Aspirin vs. Aspirin Placebo in Patients With Atrial Fibrillation and Acute Coronary Syndrome or Percutaneous Coronary Intervention) is an additional

ongoing clinical trial with randomization to warfarin plus aspirin, warfarin plus clopidogrel, apixaban plus aspirin, or apixaban plus clopidogrel. This will undoubtedly shed important light on the relative efficacy and safety of aspirin vs clopidogrel single antiplatelet therapy, as well as using warfarin double therapy rather than triple therapy as the comparator (clinicaltrials.gov ID: [NCT02415400](https://clinicaltrials.gov/ct2/show/study?term=NCT02415400)).

Conclusions

Results from recent clinical trials, including PIONEER-AF PCI and RE-DUAL PCI, have shown a significant excess of bleeding from the use of triple therapy with warfarin without any added benefit in prevention of thrombotic events. As was shown in ISAR-TRIPLE and RE-DUAL, even self-limited periods of triple therapy have resulted in a marked increase in major and minor bleeding, suggesting that the up-front risk of using aspirin in addition to clopidogrel and oral anticoagulation, even if only briefly, may be higher than previously appreciated. Based on the available data, there do not seem to be any situations in which triple therapy with warfarin is better than dual therapy. There is clear evidence of harm with the use of warfarin triple therapy. The safety of triple therapy with DOACs is less well-established, though very low-dose rivaroxaban plus DAPT may be a viable option if this dose becomes commercially available. In general, patients with atrial fibrillation who undergo PCI should be treated with a DOAC if possible plus clopidogrel or with warfarin plus clopidogrel if a DOAC is contraindicated or if the patient has tolerated long-term warfarin without significant bleeding. The duration of antiplatelet therapy on top of systemic anticoagulation should be limited; patients with acute coronary syndrome should receive 12 months of double therapy, and patients treated with elective PCI who are high risk of bleeding could be treated with 6 months of double therapy [51] (Figure 1).

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Figure 1:

Recommended algorithm for the use of antithrombotic therapy after percutaneous coronary intervention. O oral anticoagulation, C clopidogrel. We recommend that patients with ACS and low bleeding risk elective patients be treated with double antithrombotic therapy for twelve months and high bleeding risk patients for six months prior to transitioning to oral anticoagulation without antiplatelet therapy.

Table 1:

Major clinical trials comparing dual therapy with triple therapy

	Year	N	Population	Groups	Bleeding	Efficacy
WOEST	2013	573	Adults on OAC undergoing PCI	1 Warfarin + C 2 Warfarin + C + A	19.4% in patients receiving double therapy and in 44.4% receiving triple therapy (HR 0.36, 95% CI 0.26–0.50, $p<0.0001$). NNT=4 to prevent one bleeding episode.	11.1% in patients receiving double therapy vs. 17.6% in patients receiving triple therapy (HR 0.60, 95% CI 0.38–0.94, $P=0.025$); NNT 15
ISAR-TRIPLE	2015	614	Patients receiving OAC undergoing PCI	1 Warfarin + A + 6 months of C 2 Warfarin + A + 6 weeks of C	9.8% in the 6-week group vs 8.8% in the 6-month group (hazard ratio [HR]: 1.14; 95% CI: 0.68 to 1.91; $p=0.63$)	4.0% in the 6-week group vs. 4.3% in the 6-month group (HR: 0.93; 95% CI: 0.43 to 2.05; $p=0.87$)
PIONEER-AF PCI	2016	2124	Patients with non-valvular AF who had undergone PCI	1 Rivaroxaban 15mg + C 2 Rivaroxaban 2.5 mg + A + C 3 Warfarin + A + C	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; $P<0.001$	6.5% in group 1, 5.6% in group 2, and 6.0% in group 3; P values for all comparisons were nonsignificant
RE-DUAL PCI	2017	2725	Patients with AF who had undergone PCI	1 Dabigatran 110 mg + C 2 Dabigatran 150 mg + C 3 Warfarin + A + C	15.4% in the 110-mg dual-therapy group as compared with 26.9% in the triple-therapy group (HR 0.52; 95% confidence interval [CI], 0.42 to 0.63; $P<0.001$ for noninferiority; $P<0.001$ for superiority) and 20.2% in the 150-mg dual-therapy group as compared with 25.7% in the corresponding triple-therapy group (HR 0.72; 95% CI, 0.58 to 0.88; $P<0.001$ for noninferiority)	13.7% in the two dual-therapy groups combined as compared with 13.4% in the triple-therapy group (HR 1.04; 95% CI, 0.84 to 1.29; $P=0.005$ for noninferiority)

The Apixaban for Prevention of Acute Ischemic Events 2: See references 10, 11, 53, 57. HR hazard ratio, 95% CI 95% confidence interval, NNT number needed to treat, OAC oral anticoagulation, A aspirin, C clopidogrel. Bleeding compares the percentage of patients with a major bleeding episode during follow-up. Efficacy compares the percentage of patients with major adverse cardiovascular events (MACE) events during follow-up.