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Antithrombotic regimens in patients with atrial fibrillation and coronary artery disease after percutaneous coronary intervention: A focused review

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ABSTRACT

Atrial fibrillation and coronary artery disease are common comorbidities with increasing incidences worldwide. About 5–15% of atrial fibrillation patients will require coronary stenting at some point in their lives, which necessitates dual antiplatelet therapy with aspirin and a P_2Y_{12} antagonist. Triple therapy refers to the clinical scenario in which a patient is prescribed aspirin, P_2Y_{12} antagonist, and oral anticoagulant, usually in the setting of atrial fibrillation. Current guidelines on atrial fibrillation do not offer strong recommendations on triple therapy management. Furthermore, the optimal duration of dual antiplatelet therapy after percutaneous coronary intervention is evolving based on contemporary research and development of newer generation drug eluting stents, changing the necessary duration of triple therapy in patients with atrial fibrillation. This review will offer an in-depth survey of current guidelines, current evidence, and future studies regarding triple therapy in atrial fibrillation patients undergoing percutaneous coronary intervention.

1. Introduction

Atrial fibrillation (AF) is a common disease with an estimated prevalence of 2.7–6.1 million in the United States and 6.5–12.3 million in Europe [1]. The CHA_2DS_2-VASc score is currently guideline recommended to assess stroke risk, and an oral anticoagulant (OAC) is recommended for patients with a CHA_2DS_2-VASc score ≥ 1–2 to prevent thromboembolism, which is most commonly manifested by stroke [2–4]. Coronary artery disease (CAD) is a common comorbidity in AF patients, with a reported prevalence of 20–30% in Europe and as high as 60–65% among Medicare beneficiaries in the United States [2,5]. Furthermore, about 5–15% of AF patients will require coronary stenting at some point in their lives [4]. Triple therapy refers to the clinical scenario in which a patient is prescribed aspirin, P_2Y_{12} antagonist, and OAC, usually in the setting of AF. Traditional triple therapy consists of aspirin, clopidogrel, and vitamin K antagonist (VKA). However, several newer P_2Y_{12} antagonists with more potent antiplatelet effects have become more commonly prescribed, particularly in the setting of acute coronary syndrome (ACS) and percutaneous coronary intervention (PCI) [6,7]. Additionally, non-VKA OACs, or the direct oral anticoagulants (DOACs), have been studied compared to VKAs, with increased use in contemporary practice for stroke risk reduction in AF patients [8–11]. The main complication with triple therapy is clinically significant bleeding [2,3,12,13]. There remains controversy on how to optimize triple therapy to minimize stent thrombosis as well as bleeding complications. This review will offer an in-depth survey of current guidelines, current evidence, and future studies regarding triple therapy in AF patients undergoing PCI.

2. Review of guidelines

The following guidelines discuss triple therapy: (1) 2016 European Society of Cardiology guidelines on AF, (2) 2014 European joint consensus document on AF and PCI, (3) 2014 American College of Cardiology/American Heart Association (ACC/AHA) non-ST-segment elevation myocardial infarction (NSTEMI) guidelines, (4) 2013 ACC/AHA ST-segment elevation myocardial infarction (STEMI) guidelines [3,4,14,15]. The 2016 ACC/AHA guidelines on dual antiplatelet therapy (DAPT) and 2014 American College of Cardiology/American Heart Association/Heart Rhythm Society (ACC/AHA/HRS) guidelines on AF briefly mention triple therapy but do not offer formal recommendations [2,16]. The 2012 ACC/AHA guidelines on stable ischemic heart disease and the 2014 ACC/AHA focused update on stable ischemic heart disease do not discuss triple therapy [17,18]. The guideline recommendations are summarized in Table 1.

The 2016 European guidelines on AF acknowledge that the optimal combination of antithrombotic therapy or duration of combination therapy for AF patients undergoing PCI is unknown [4]. The recommendations

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Table 1
Guideline recommendations on triple therapy in atrial fibrillation.

Class	2016 European Society of Cardiology Guidelines on AF [4]	2014 European Consensus on AF and PCI [3]	2014 ACC/AHA Guidelines on NSTEMI [14]	2013 ACC/AHA Guidelines on STEMI [15]
I	OAC monotherapy 12 months after ACS or PCI (6 months if high bleeding risk after elective PCI)	None	Prescribe PPIs in patients with NSTEMI with history of GI bleeding who require triple therapy Minimize triple therapy to the extent possible to limit risk of bleeding	Anticoagulant therapy with a VKA should be provided to patients with STEMI and AF with $CHADS_2$ score ≥ 2 Minimize triple therapy to extent possible to limit risk of bleeding
IIa	Minimize duration of triple therapy, balancing risk of recurrent coronary events and bleeding Elective PCI + stable CAD ➔ 1 month of triple therapy ACS + stent ➔ 1–6 months of triple therapy ACS + no stent ➔ up to 12 months of dual therapy with OAC + antiplatelet After completion of triple therapy, dual therapy with OAC + antiplatelet until 12 months after ACS or PCI (6 months if high bleeding risk after elective PCI)	OAC monotherapy 12 months after ACS or PCI PPI should be considered in patients on OAC + antiplatelet Elective PCI + stable CAD ➔1–6 months of triple therapy ACS ➔ 1–6 months of triple therapy After completion of triple therapy, dual therapy with OAC + antiplatelet until 12 months after ACS or PCI When VKA is given in combination with clopidogrel and/or low dose aspirin, target INR of 2.0 to 2.5	PPI is reasonable in patients with NSTEMI without history of GI bleeding who require triple therapy	None
IIb	Dual therapy with any OAC plus clopidogrel 75 mg/day may be considered as an alternative to initial triple therapy in selected patients	Dual therapy with any OAC plus clopidogrel 75 mg/day may be considered as an alternative to initial triple therapy in selected patients ACS ➔ consider 6–12 months of triple therapy if low bleeding risk (HAS-BLED score 0–2) OAC + antiplatelet beyond 12 months after ACS in select cases (i.e. stenting of left main, proximal LAD, proximal bifurcation, recurrent MIs, etc.) New generation DES may be preferred over BMS in patients with low bleeding risk (HAS-BLED score of 0–2) When DOAC is combined with clopidogrel and/or low dose aspirin, consider the lower tested dose for stroke prevention in AF (dabigatran 110 mg BID, rivaroxaban 15 mg QDAY, apixaban 2.5 mg BID) Consider prasugrel or ticagrelor in combination with OAC under certain circumstances (i.e. definite stent thrombosis while on clopidogrel, aspirin, and OAC)	Targeting OAC therapy to a lower INR of 2.0 to 2.5 may be reasonable in patients who are receiving aspirin and P_2Y_{12} inhibitor	Targeting OAC therapy to a lower INR of 2.0 to 2.5 may be reasonable in patients who are receiving aspirin and P_2Y_{12} inhibitor
III	None	Prasugrel and ticagrelor should not be part of triple therapy	None	None

ACC/AHA, American College of Cardiology/American Heart Association; ACS, acute coronary syndrome; AF, atrial fibrillation; BID, twice a day; BMS, bare metal stent; CAD, coronary artery disease; DES, drug eluting stent; GI, gastrointestinal; INR, international normalized ratio; LAD, left anterior descending artery; MI, myocardial infarction; NSTEMI, non-ST segment myocardial infarction; OAC, oral anticoagulant; PCI, percutaneous coronary intervention; PPI, proton pump inhibitor; QDAY, daily; STEMI, ST-segment myocardial infarction; VKA, vitamin K antagonist.

build off of the 2014 European consensus document on AF and PCI, which recommends a stepwise algorithm that consists of (1) stroke risk stratification with CHA_2DS_2-VASc score, (2) bleeding risk stratification with HAS-BLED score, and (3) differentiating between stable CAD versus ACS [3]. Using this algorithm, eight different antithrombotic regimens are possible. Table 2 summarizes the risk factors assessed with the CHA_2DS_2-VASc and HAS-BLED scores. Per recommendations, a CHA_2DS_2-VASc score of 1 is considered moderate risk, so an OAC is recommended [3]. The 2016 European guidelines simplify the algorithm by only incorporating two variables: (1) ACS vs. elective PCI, (2) high vs. low bleeding risk without mention of using the HAS-BLED score [4]. European guideline recommendations regarding triple therapy regimens are listed in Table 1.

In contrast, the 2014 ACC/AHA/HRS guidelines on AF recommend anticoagulation for CHA_2DS_2-VASc score ≥ 2 and suggest anticoagulation may be considered in patients with a CHA_2DS_2-VASc score of 1 [2]. The 2014 ACC/AHA/HRS guidelines on AF also do not recommend using HAS-BLED score to assess bleeding risk due to insufficient clinical utility [2]. ACC/AHA guidelines on NSTEMI and STEMI do not specify optimal duration of triple therapy for patients on OAC with an acute myocardial infarction (MI) [14,15].

The 2014 European consensus document on AF and PCI recommends new generation drug-eluting stents (DES) over bare metal stents (BMS) in patients with low bleeding risk (HAS-BLED score ≤ 2), but the 2014 ACC/AHA/HRS guidelines on AF, 2014 ACC/AHA guidelines on NSTEMI, and 2013 ACC/AHA guidelines on STEMI suggest that a BMS may be advantageous to DES due to potentially shorter duration of triple therapy [2,3,14,15].

In spite of the differences in guideline recommendations, there are overlapping recommendations between the European and ACC/AHA

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