Triple Antithrombotic Therapy in Atrial Fibrillation Patients With an Indication for Oral Anticoagulation Undergoing Percutaneous Coronary Intervention

A Case-Based Review of the Current Evidence

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Atrial fibrillation (AF) is a growing problem, affecting 5.2 million people in the United States in 2010, with a prevalence that is expected to increase to over 12 million by 2030.[1,2] The standard of care for stroke prevention in such patients at increased risk, as indicated by a congestive heart failure, hypertension, age ≥75 y (doubled), diabetes mellitus, prior stroke or TIA or thromboembolism (doubled), vascular disease, age 65–74 y, sex category (CHA_2DS_2-VASc) score[3] ≥1, is anticoagulation with a vitamin K antagonist (VKA) or novel oral anticoagulant (NOAC).[4] In addition, patients with AF have a high risk of concomitant coronary artery disease (CAD), and when percutaneous coronary intervention (PCI) is required, treatment with aspirin and a platelet P2Y12 receptor inhibitor also becomes indicated.[5–7] In such cases, the risk of thromboembolic events and stent thrombosis (ST) after PCI must be weighed against the risk of major bleeding.[8–11] Newer, more potent antiplatelet therapy and novel anticoagulants have emerged, thus, making the decision of triple therapy (TT) even more challenging. The optimal antithrombotic therapy for AF patients undergoing PCI is as yet unknown. For many primary care physicians and general cardiologists, the duration, benefits, and bleeding risks of TT in AF patients is unclear.

We describe a clinical case of a patient with AF undergoing PCI and discuss medical management for such patients with an emphasis on the recent available data.

Case Presentation

A 77-year-old woman with permanent AF, diabetes mellitus, dyslipidemia, who was receiving warfarin to prevent stroke presented to the outpatient clinic with progressive chest pain for the past 3 months. She was a former smoker and was carefully taking her medication, which included β-blockers, statins, metformin, and warfarin, with stable international normalized ratio (INR) results. Her ECG showed left ventricular hypertrophy and no significant ischemic changes. Echocardiography was normal with preserved left ventricular systolic function. She subsequently underwent an exercise treadmill test that was strongly positive at 5.3 metabolic equivalents. Troponin was normal, and the patient had no renal or liver dysfunction. She was referred for coronary angiography, which revealed severe stenosis of the right coronary and posterior descending artery (Figure 1). The patient underwent an uncomplicated PCI with implantation of 3 drug-eluting stents (DES).

In light of the patient's high risk for an embolic event, as assessed by a CHA_2DS_2-VASc score of 4 and a low bleeding risk, with a HAS-BLED (hypertension, abnormal renal and liver function, stroke, bleeding, labile INRs, elderly, drugs or alcohol) score[12] of 2 (Table 1), she received medical therapy with aspirin 81 mg, clopidogrel 75 mg, and warfarin, targeting an INR of 2.0 to 2.5 for 6 months, at which time aspirin was to be discontinued. She was discharged the day after PCI.

Two months later, she was emergently admitted to the intensive care unit with an upper gastrointestinal bleed because of a gastric ulcer, confirmed by endoscopy. She was treated with intravenous proton-pump inhibitors (PPI) and combined (thermal+epinephrine) endoscopic therapy. At discharge, aspirin was discontinued and an oral PPI added. Antithrombotic therapy with warfarin and clopidogrel was continued for another 10 months before stopping clopidogrel.

Discussion

Dr Picard: How common are patients like the one described and what are the therapeutic challenges for such patients undergoing PCI?

Dr Asgar: Approximately 5% to 8% of patients undergoing PCI and stenting have an indication for long-term oral anticoagulation (OAC) because of AF.[7,8] Obviously, the main concern is to prevent death and disability for our patients. The challenge is finding the optimal balance between preventing thromboembolic events, such as thromboembolic stroke without increasing bleeding risk post-PCI. Chronic OAC is recommended in patients with AF and a CHA_2DS_2-VASc score ≥1,[4] and ≈30% of AF patients have concomitant CAD.

Received September 8, 2015; accepted November 5, 2015.

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(*Circ Cardiovasc Interv*. 2015;8:00-00. DOI: 10.1161/CIRCINTERVENTIONS.115.003217.)

The risk of thromboembolic stroke is significant and increases with the presence of other comorbidities. Clinical scores designed to evaluate stroke risk, such as CHA_2DS_2-VASc, estimate a risk of stroke of 3.2% per year for those with a score >2, increasing to >6.7% per year if the score is superior to 5 (Table 1).[3] Therefore, anticoagulation must always be part of the therapy. The challenge lies in combining anticoagulant and antiplatelet therapy, which increases hemorrhagic risk.[11] Our goal is to minimize the risk of major hemorrhage by adapting the choice and duration of antiplatelet and perhaps antithrombotic therapy. At present, more potent antiplatelet therapies, such as prasugrel and ticagrelor,[13] are available, but their combination with antithrombotic therapy is not recommended and preference is generally given to use of clopidogrel. The mainstay of antithrombotic therapy has long been VKA, such as warfarin, which has limitations, including labile digestive absorption and the cytochrome interactions, resulting in instability in the level of anticoagulation, thereby, increasing risk of intracranial hemorrhage. The NOACs have been proven to have the same hemorrhagic profile risk as compared with VKA,[14] with potentially reduced intracranial bleeding. There is currently no data available on patients undergoing PCI with NOACs; however, several trials are underway (PIONEER AF-PCI [An 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], REDUAL-PCI [Evaluation of Dual Therapy With Dabigatran vs Triple Therapy With Warfarin in Patients With NVAF That Undergo a PCI With Stenting], AUGUSTUS [Study Apixaban to Vitamin K Antagonist for the Prevention of Stroke or Systemic Embolism and Bleeding in Patients With Non-valvular Atrial Fibrillation and Acute Coronary Syndrome/Percutaneous Coronary Intervention]).

Dr Picard: Given the bleeding risk that you mention, when would you prefer percutaneous revascularization over surgical revascularization?

Dr Asgar: Even if the bleeding risk is increased in these patients, the decision of revascularization is based on classical recommendations.[15,16] No specific randomized controlled trial (RCT) has been done on revascularization of patients under OAC. Surgical revascularization is generally recommended in preference to PCI to improve survival in patients with diabetes mellitus and multivessel CAD for which revascularization is likely to improve survival (3-vessel CAD or complex 2-vessel CAD involving the proximal left anterior descending artery), particularly if a left internal mammary artery graft can be anastomosed to the left anterior descending artery, provided the patient is a good candidate for surgery. Currently, when surgical revascularization is considered, concomitant surgical left atrial appendage (LAA)[17] obliteration may be considered to reduce stroke risk[18] in coronary artery bypass graft patients with a history of AF, but randomized studies are needed to further clarify this issue. Removal or closure of the LAA should be considered as an adjunct to anticoagulation and not as an alternative for anticoagulant therapy until more and longer term data are available.

Dr Tadros: Current guidelines still recommend bare metal stents placement in patients with AF. For which patients would you choose DES over BMS?

Dr Asgar: Although the use of DES has decreased the rate of restenosis in many patient populations when compared with BMS,[19] little is known about their performance in patients with AF undergoing PCI. Current recommendations on the optimal choice of stent type and strategy of antithrombotic therapy in this high-risk subset of patients are derived mainly from small retrospective single-center studies, observational studies, and expert opinion statements, providing a weak level of evidence.[4,20–22] Nevertheless, there was a shift for DES in the latest European recommendations.[6,16] New-generation DES should be preferred over BMS to reduce restenosis rates and optimize target vessel revascularization, particularly in patients at low bleeding risk (HAS-BLED score 0–2). In the high bleeding-risk patient (HAS-BLED score ≥3) or in low restenosis-profile lesions, BMS can be used to safely reduce the duration of antithrombotic therapy.

Dr Tadros: Should we systematically consider bleeding risk scores before implanting BMS or DES?

Dr Asgar: Several scores has been validated to assess bleeding risk in AF patients, and the most widespread is the HAS-BLED score (Table 1).[12,23] It estimates the risk for major bleeding and is based on the presence of some high-risk features. More than the assessment of bleeding risk, the HAS-BLED score has also demonstrated some predictive value for cardiovascular events and mortality in anticoagulated patients with AF. The data are consistent with the relationship between thrombosis and bleeding and confirm that the number of bleeding and thrombotic events is higher in patients with high comorbidities at baseline.[12] Therefore, bleeding risk should always be considered before the patient enters the catheterization laboratory. The HAS-BLED scores range from 0 to 9, with scores of ≥3 indicating a high risk of bleeding, for which caution and regular follow up of the patient are recommended. The higher the risk, the more measures should be taken to avoid and prevent bleeding, such as use of low-dose aspirin use (≤100 mg), avoidance of nonsteroidal anti-inflammatory agent, the standardized use of a radial approach, smaller sheath size, BMS use, routine use of PPI, utilization of a target INR range of 2.0 to 2.5,[24] the choice and dose of antithrombotics and P2Y12 inhibitors, and avoidance of all of the following: use of glycoprotein IIb/IIIa inhibitors, periprocedural bridging with low molecular weight heparin, and crossing over from 1 antithrombotic to another, if not strictly indicated.[4,6,25,26]

Dr Picard: In the case of our patient, what do the Guidelines say about antithrombotic therapy?

Dr Asgar: Actual guidelines are disparate and complex. Moreover, most of them rely more on expert opinions than on solid evidence.[4,6,7,16] Recently, a consensus document on the management of antithrombotic therapy in AF patients presenting with acute coronary syndrome or undergoing PCI was recently published.[6] It is more up-to-date than the American recommendations,[7] but still largely opinion-based. The suggested initial therapies are summarized in Table 2. For our patient, they would have recommended triple (with OAC, aspirin, and clopidogrel) or dual (OAC and clopidogrel) therapy in selected patients for 6 months, dual therapy (with OAC and aspirin or clopidogrel) for another 6 months, and OAC monotherapy after 12 months.

Dr Tadros: On which evidence would you give only dual therapy with OAC and clopidogrel? Is the risk of ST a major concern?

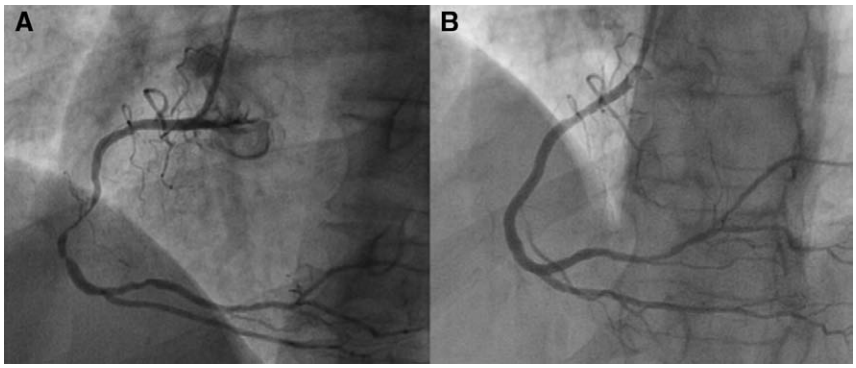

Figure 1. Right coronary artery angiography. **A**, Severe stenosis on mid right coronary artery and posterior descending artery. **B**, Final result after right coronary and posterior descending arteries stenting.

Dr Asgar: Patients are started on TT because of a concern for thrombotic events: VKA given alone is not effective to prevent ST, whereas dual antiplatelet therapy (DAPT) is inferior to VKA in the prevention of thromboembolism in AF patients. The first nonrandomized studies of TT showed a protection from ischemic events with no prohibitive excess bleeding, compared to other regimens.[27,28] These studies were limited by the fact that they were single-center nonrandomized data but did suggest that a short period of TT was possible and became the basis of recommendations for a short duration of TT. The only RCT comparing dual versus TT was the What Is the Optimal Antiplatelet and Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary Stenting (WOEST) trial[9] of 573 patients treated with VKA undergoing PCI in an open-label, intention-to-treat design. Patients were randomized to either double therapy (VKA and clopidogrel 75 mg daily, with aspirin stopped immediately after PCI) or TT (VKA, clopidogrel, and aspirin 80 mg daily). At 1-year follow-up, the primary end point of all thrombolysis in myocardial infarction bleeding was significantly reduced in the dual-therapy arm (19.4% in the dual-therapy group versus 44.4% in patients treated with TT; hazard ratio [HR], 0.36; 95% confidence interval [CI], 0.26–0.50; $P<0.0001$). Of note, there was a significant reduction in minimal and minor bleeding, while major bleeding was also numerically lower, but did not reach statistical significance ($P=0.159$). Clinical ischemic events were a secondary end point (major adverse cardiac and cerebrovascular events defined as the composite of death, myocardial infarction, stroke, systemic embolism, target vessel revascularization, and ST), and results suggested that these were not increased by eliminating aspirin (11.1% for patients receiving dual therapy versus 17.6% of patients receiving TT; HR, 0.60; 95% CI, 0.38–0.94; $P=0.025$). In fact, most end points showed lower numeric rates in the dual-therapy arm, and total mortality was significantly reduced.[9]

Since the publication of WOEST, multiple registries have also demonstrated the safety and efficacy of double therapy versus TT and were included in a recent meta-analysis by Gao et al[29] that demonstrated that in patients taking OAC and undergoing

Table 1. Assessment of Stroke (CHA_2DS_2-VASc)[3] and Bleeding (HAS-BLED)[12] Risk Stratification for Subjects With Nonvalvular AF

CHA2DS2-VASc Scoring System	Adjusted Stroke Rate (% per Year) Based on CHA2DS2-VASc Score			HAS-BLED Scoring System	Adjusted Major Bleeding Rate (% per Year) Based on HAS-BLED Score		
Congestive HF	+1	0	0%	Hypertension (systolic blood pressure >160 mm Hg)	+1	0	1.13%
Hypertension	+1	1	1.3%	Abnormal renal and liver function* (1 point each)#8232;	+1 or +2	1	1.02%
Age ≥75 y	+2	2	2.2%	Stroke	+1	2	1.88%
Diabetes mellitus	+1	3	3.2%	Bleeding tendency/predisposition*	+1	3	3.74%
Previous stroke/TIA/TE	+2	4	4.0%	Labile INRs (if on warfarin)*	+1	4	8.70%
Vascular disease	+1	5	6.7%	Elderly (eg, age >65 y)	+1	5	12.50%
Age 65–74 y	+1	6	9.8%	Drugs or alcohol (1 point each)*	+1 or +2	6	Insufficient data
Sex category (ie, female sex)	+1	7	9.6%			7	Insufficient data
Maximum score	9	8	6.7%	Maximum score	9	8	Insufficient data
		9	15.20%			9	Insufficient data

Adjusted stroke rate scores are based on data from Lip et al[3] and bleeding on data from Pisters et al.[12] Actual rates of stroke and bleeding in contemporary cohorts might vary from these estimates. AF indicates atrial fibrillation; CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥75 y (doubled), diabetes mellitus, prior stroke or TIA or thromboembolism (doubled), vascular disease, age 65–74 y, sex category; HAS-BLED, hypertension, abnormal renal and liver function, stroke, bleeding, labile INRs, elderly, drugs or alcohol; HF, heart failure; INR, international normalized ratio; MI, myocardial infarction; PAD, peripheral artery disease; TE, thromboembolism; and TIA, transient ischemic attack.[3]

*Abnormal renal function is classified as the presence of chronic dialysis, renal transplantation, or serum creatinine ≥200 mmol/L. Abnormal liver function is defined as chronic hepatic disease (eg, cirrhosis) or biochemical evidence of significant hepatic derangement (bilirubin 2–3× the upper limit of normal, in association with aspartate aminotransferase/alanine aminotransferase/alkaline phosphatase 3× the upper limit normal, etc), history of bleeding or predisposition (anemia), labile INR (ie, time in therapeutic range <60%), concomitant antiplatelets or nonsteroidal anti-inflammatory drugs, or excess alcohol.

Table 2. Adapted From ESC Guidelines–Recommended Antithrombotic Strategies Following Coronary Stent Implantation in Patients in AF With Moderate to High Thromboembolic Risk, in Whom OAC Is Required

Hemorrhagic Risk	Stroke Risk	Clinical Setting	Recommendations
Low or moderate (HAS-BLED 0–2)	Moderate (CHA_2DS_2-Vasc=1 in males)	Stable CAD	At least 4 wk (no longer than 6 mo) of triple therapy of OAC+aspirin 75–100 mg/d+clopidogrel 75 mg/d
			Up to 12 mo OAC+clopidogrel 75 mg/d (or aspirin 75–100 mg/d)
			Lifelong OAC
	High (CHA_2DS_2-Vasc≥2)	Stable CAD	At least 4 wk (no longer than 6 mo) of triple therapy of OAC+aspirin 75–100 mg/d+clopidogrel 75 mg/d
			Up to 12 mo OAC+clopidogrel 75 mg/d (or aspirin 75–100 mg/d)
			Lifelong OAC
	Moderate (CHA_2DS_2-Vasc=1 in males)	ACS	6 mo of triple therapy of OAC+aspirin 75–100 mg/d+clopidogrel 75 mg/d
			Up to 12 mo OAC+clopidogrel 75 mg/d (or aspirin 75–100 mg/d)
			Lifelong OAC
	High (CHA_2DS_2-Vasc≥2)	ACS	6 mo of triple therapy of OAC+aspirin 75–100 mg/d+clopidogrel 75 mg/d
			Up to 12 mo OAC+clopidogrel 75 mg/d (or aspirin 75–100 mg/d)
			Lifelong OAC
High (HAS-BLED≥3)	Moderate (CHA_2DS_2-Vasc=1 in males)	Stable CAD	12 mo OAC+clopidogrel 75 mg/d
			Lifelong OAC
	High (CHA_2DS_2-Vasc≥2)	Stable CAD	4 wk of triple therapy of OAC+aspirin 75–100 mg/d+clopidogrel 75 mg/d
			Up to 12 mo OAC+clopidogrel 75 mg/d (or aspirin 75–100 mg/d)
			Lifelong OAC
	Moderate (CHA_2DS_2-Vasc=1 in males)	ACS	4 wk of triple therapy of OAC+aspirin 75–100 mg/d+clopidogrel 75 mg/d
			Up to 12 mo OAC+clopidogrel 75 mg/d (or aspirin 75–100 mg/d)
			Lifelong OAC
	High (CHA_2DS_2-Vasc≥2)	ACS	4 wk of triple therapy of OAC+aspirin 75–100 mg/d+clopidogrel 75 mg/d
			Up to 12 mo OAC+clopidogrel 75 mg/d (or aspirin 75–100 mg/d)
			Lifelong OAC

PPI should be considered when aspirin is used. Newer generation of DES should be preferred over BMS in patients at low risk for bleeding. OAC can be either VKA (INR 2–2.5) or non-VKA agent at lower dose (Dabigatran 110 mg BID; Rivaroxaban 15 mg OD; Apixaban 2.5 mg BID). ACS indicates acute coronary syndrome; BMS, bare metal stent; CAD, coronary artery disease; DES, drug-eluting stent; HAS-BLED, hypertension, abnormal renal and liver function, stroke, bleeding, labile INRs, elderly, drugs or alcohol; INR, international normalized ratio; OAC, oral anticoagulation; PPI, proton pump inhibitors; and VKA, vitamin K antagonist.

PCI, treatment with OAC plus clopidogrel was associated with at least similar efficacy and safety compared with TT.

Dr Picard: Then why don't the guidelines recommend dual therapy with OAC and clopidogrel?

Dr Asgar: First, the reluctance to change the guidelines are based on the lack of RCTs and the limitations of the WOEST trial: the population size was too small to evaluate major thrombotic outcomes, the relatively low number of patients with AF (70%), the absence of significant differences in major bleeding, the low rate of PPI use at baseline, radial approach in only 26% of cases, the low rate of BMS use (31%), and the unchanged target of INR (2–3, instead of 2–2.5 recommended in latest available guidelines 29). Second, it is still difficult to produce a general recommendation because of the complexity of these patients with differing comorbidities, bleeding, and thrombotic risks. An individual patient-centered approach is preferred, as suggested in the European consensus document.[6] Nevertheless, in light of the findings from WOEST and registry data,[29] there seems to be an increasing amount of data supporting the use of dual therapy and OAC in selected AF patients rather than TT after PCI.

Dr Picard: What about the new antiplatelet agents like prasugrel and ticagrelor?

Dr Asgar: The newer antiplatelet drugs are more effective than clopidogrel, but are not safer in terms of bleeding.[13] In an exploratory study, Sarafoff et al[30] found increased bleeding events with prasugrel compared with clopidogrel but no significant difference in ischemic end points. Interestingly, most of the patients on prasugrel were switched because of an impaired response to clopidogrel, without any impact on ischemic events. Thus, in the setting of TT, platelet function–tailored approach may not be a good option. We do not have data yet on the combinations of VKA plus prasugrel or ticagrelor alone or TT with ticagrelor in AF patients undergoing PCI, and one could assume that

combining these more potent platelet inhibitors with VKA could lead to more bleeding events. Nevertheless, the MANJUSRI trial (NCT02206815; Safety of Ticagrelor Plus Warfarin Versus Clopidogrel+Aspirin+Warfarin in Patients With Persistent or Permanent Atrial Fibrillation and Undergoing PCI-S: A Randomized, Open, Controlled, Parallel Group, Multi-center Trial) will evaluate the combination therapy of warfarin and ticagrelor (90 mg/bid) versus TT (clopidogrel+aspirin+warfarin) in patients with persistent or permanent AF after PCI in a randomized, open-labeled, controlled, multicenter fashion. Until then, it may be prudent to avoid prasugrel and ticagrelor when using TT because of the potential bleeding risks.

Dr Tadros: The availability and prevalence of novel anticoagulants makes the decision even more unclear. What would you suggest for a patient treated with an NOAC undergoing PCI?

Dr Asgar: The use of NOACs for stroke prevention in AF is increasing. Data from RCTs of NOACs in nonvalvular AF have demonstrated equivalent or increased reduction in stroke with lower rates of intracranial bleeding.[31] The data on NOACs in combination with antiplatelet agents comes from post hoc analysis of randomized trials.[32,33] An analysis of data from the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial found that ≈38% (n=6952) of patients randomized had received antiplatelet therapy with predominantly aspirin, clopidogrel, or both at some point during the study. In terms of safety, there was no significant difference in major bleeding between patients on dabigatran 150 mg and antiplatelet therapy or warfarin combined with antiplatelet therapy (HR, 0.93; 95% CI, 0.76–1.12 for patients with antiplatelets; HR, 0.94; 95% CI, 0.78–1.15 for patients without antiplatelets; *P* for interaction =0.875).[32,33] With respect to intracranial hemorrhage, however, dabigatran was superior to warfarin, regardless of whether patients had been using antiplatelet treatment (HR, 0.47; 95% CI, 0.28–0.80) or not (HR, 0.36; 95% CI, 0.21–0.63; *P* for interaction =0.526). The study contained a small number of patients on DAPT (4.5%, n=812), and the risk of major bleeding was higher in this subgroup, with the highest risk seen in those on warfarin and lowest in those on lower dose dabigatran. An analysis of ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation), which randomized patients to apixaban or warfarin, and concomitant aspirin use found lower bleeding rates in those treated with apixaban and aspirin.[33] Of note, patients with clopidogrel or DAPT were not included.

Based on these results, with stable patients undergoing PCI already on an NOAC, I would continue it. I would be concerned

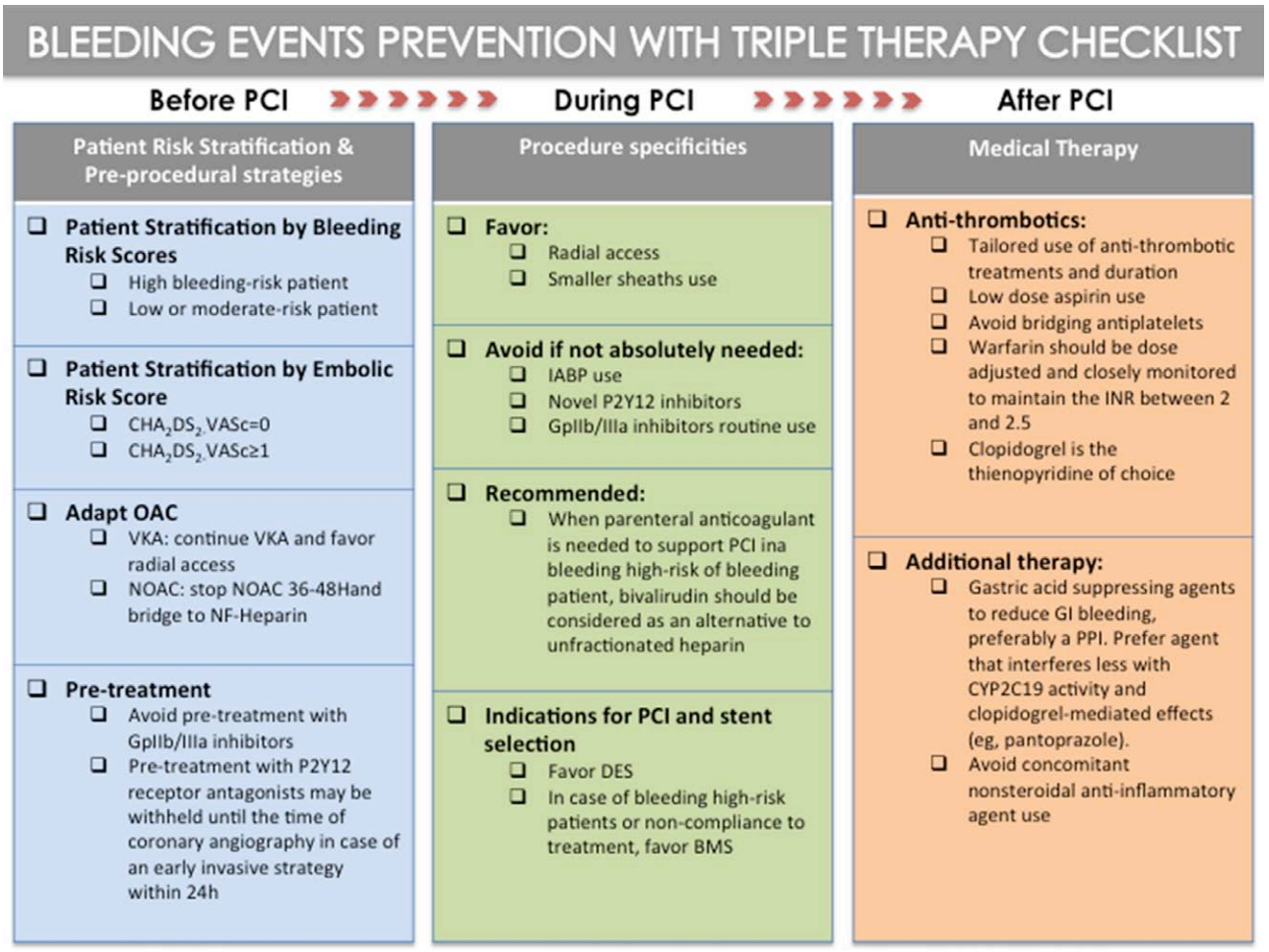

Figure 2. Bleeding events prevention checklist. BMS indicates bare metal stent; CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥75 y (doubled), diabetes mellitus, prior stroke or TIA or thromboembolism (doubled), vascular disease, age 65–74 y, sex category; DES, drug-eluting stent; GI, gastrointestinal; IABP, intra-aortic balloon pump; INR, international normalized ratio; NOAC, novel oral anticoagulant; PCI, percutaneous coronary intervention; PPI, proton pump inhibitors; and VKA, vitamin K antagonist.

about bleeding and may consider adjusting the dose of warfarin or NOAC depending on the patient's underlying bleeding risk.

Dr Picard: We will likely have part of the answer soon. Other trials are underway to evaluate the role of NOACs versus VKA in AF patients undergoing PCI for either stable CAD or acute coronary syndrome, including the REDUAL-PCI trial (NCT02164864) investigating the effects of dabigatran as the anticoagulant in TT, the PIONEER AF-PCI trial investigating rivaroxaban (NCT01830543), and the AUGUSTUS trial evaluating apixaban (NCT02415400). This data will provide key insights into the potential of newer agents. The only downside may be that their designs compare NOACs in combination with either clopidogrel alone or DAPT versus TT using warfarin, a P2Y12 inhibitor, and aspirin but not the dual therapy of the WOEST trial. Therefore, there will not be a direct comparison of their efficacy and safety compared with the dual therapy clopidogrel and warfarin.

Dr Tadros: Data seems to be controversial about the duration of double antiplatelet therapy in patients. What about TT?

Dr Asgar: Duration of DAPT was largely discussed over the past months as a result of the DAPT trial (12 or 30 months of DAPT after DES).[34] Moreover, the recent meta-analysis performed by Palmerini et al[35] of 8180 patients treated with DES, short-term DAPT was associated with similar rates of major adverse cardiac events but lower rates of bleeding compared with prolonged DAPT. Looking at these data, you can easily understand that the duration of TT is a matter of particular importance because the bleeding risk is even higher with TT. The only available RCT on this question is the recent Intracoronary Stenting and Antithrombotic Regimen–Testing of a 6-Week Versus a 6-Month Clopidogrel Treatment Regimen in Patients With Concomitant Aspirin and Oral Anticoagulant Therapy Following Drug-Eluting Stenting (ISAR-TRIPLE) trial,[36] which randomized a total of 614 patients receiving concomitant aspirin and OAC to either 6-week clopidogrel therapy (n=307) or 6-month clopidogrel therapy (n=307). The trial was designed to show superiority of 6 weeks of TT compared with 6 months and assumed an event rate (composite of death, myocardial infarction, definite ST, stroke, or thrombolysis in myocardial infarction major bleeding) of 10% in the 6-month treatment arm with a hypothesized 60% reduction in the 6-week arm. The primary end point occurred in 30 patients (9.8%) in the 6-week group compared with 27 patients (8.8%) in the 6-month group (HR, 1.14; 95% CI, 0.68–1.91; *P*=0.63). There were no significant differences for the secondary combined ischemic end point of cardiac death, myocardial infarction, definite ST, and ischemic stroke;(12 [4.0%] versus 13 [4.3%]; HR, 0.93; 95% CI, 0.43–2.05; *P*=0.87) or the secondary bleeding end point of thrombolysis in myocardial infarction major bleeding (16 [5.3%] versus 12 [4.0%]; HR, 1.35; 95% CI, 0.64–2.84; *P*=0.44). The study failed to achieve the primary end point and was limited by low clinical event rates. The study has been interpreted by some as proof that the duration of TT can be safely shortened; however; we caution against assuming noninferiority from an underpowered trial designed to shown superiority.

Dr Picard: What about after 1 year? Should we continue OAC alone or with an antiplatelet agent?

Dr Asgar: That's another unanswered question. In the absence of RCT, we have to look at registries. The Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) Registry[37] included 7347 patients under OAC and showed that combination of VKA and aspirin was associated with significantly increased risk for bleeding without a clear reduction of major adverse cardiac and cerebrovascular events. Another recent large registry, conducted by Lamberts et al,[38] demonstrated that in AF patients with stable CAD, the addition of antiplatelet therapy to VKA therapy was not associated with a reduction in risk of recurrent coronary events or thromboembolism, whereas risk of bleeding was increased significantly. The common practice of adding antiplatelet therapy to oral VKA anticoagulation in patients with AF and stable CAD warrants reassessment.

Dr Tadros: Our patient had unfortunately a bleeding event. Do we have ways to prevent major bleeding events and what are they?

Dr Asgar: First of all, before PCI, stratification of bleeding-risk and embolic-risk scores is important. Added to that stratification, OAC in nonemergent PCI should be adapted depending of which class of OAC is used (VKA could be pursued with favor of radial access, and NOAC should be stopped 24–48 hours before PCI). When possible, pretreatment with P2Y12 receptor antagonists should be withheld until the time of coronary angiography in case of an early invasive strategy within 24 hours. Second, in the catheterization laboratory, procedural details can help to decrease peri-procedure bleeding, such as the use of radial access, smaller sheaths, and weighing the indication of DES instead of BMS. Finally, after PCI, tailored use of antithrombotic therapy should be determined in accordance with the available evidence, low-dose of aspirin (if introduced); warfarin dose should be adjusted and closely monitored to maintain the INR between 2 and 2.5; routine PPI use is highly recommended[6,16] when using TT; and doctor and pharmacist should avoid any nonsteroid anti-inflammatory administration.[26] Ideally, PPI with less cytochrome P450 2C19 (CYP2C19) inhibitory activity, as pantoprazole, should be used. The plasma concentrations of the clopidogrel active metabolite and the degree of platelet inhibition are less than observed with clopidogrel alone but greater than observed with omeprazole.[39] These recommendations are summarized in Figure 2.

Dr Tadros: How would you manage our patient medical therapy after this acute bleeding event?

Dr Asgar: Given the available data, I would stop aspirin, continue clopidogrel for another 10 months, and then stop or continue clopidogrel, depending on the clinical course of the patient.

Dr Picard: Could we consider left appendage closure in patients with AF and high bleeding risk undergoing PCI?

Dr Asgar: Excellent question. Although we lack definitive data to support such a decision, the Watchman device (Boston Scientific) is now Food and Drug Administration-approved for closure of the LAA with a relatively wide indication:

"…This device is indicated to reduce the risk of thromboembolism from the LAA in patients with nonvalvular AF who:

- Are at increased risk for stroke and systemic embolism based on $CHADS_2$ or CHA_2DS_2-VASc scores and are recommended for anticoagulation therapy
- Are deemed by their physicians to be suitable for warfarin
- Have an appropriate rationale to seek a nonpharmacological alternative to warfarin, taking into account the safety and effectiveness of the device compared to warfarin."

Given this approval, LAA closure with the Watchman device could be performed in such patients; however, ideally, randomized trial or registry data would be needed to support a recommendation of routine LAA closure in such patients.

Clinical Outcome

The patient course remained uneventful after 12 months of dual therapy. Therefore, given her HAS-BLED score of 3, we decided to stop clopidogrel and remain with OAC alone. At 1-year follow-up, she remained well, free of angina or other bleeding complications.

Conclusions

AF is a common condition in the aging population that also is at risk for CAD. Management of such patients is challenging, particularly in the case of those patients on antithrombotic therapy requiring antiplatelet therapy after coronary intervention. Despite accumulating data on duration of therapy and bleeding risks, the optimal antithrombotic therapy for patients on chronic OAC after PCI with stent implantation is unclear. New evidence, including an RCT and large registries, suggest that the combination of VKA and clopidogrel without aspirin may improve clinical outcomes in comparison with TT. NOACs are probably as effective as VKA as part of TT or dual therapy; however, bleeding may be significant in the case of DAPT. Currently, neither ticagrelor nor prasugrel is recommended as part of TT in AF patients after PCI. Results of current RCTs will guide cardiologists to the optimal antithrombotic regimen for this growing group of patients. In the meantime, careful assessment of both thrombotic and bleeding risk and individualized decision-making are paramount to ensure the best patient outcomes.

Acknowledgments

All of the authors contributed to the literature review, manuscript drafts, and reviewed and approved the final manuscript.

Sources of Funding

Dr Picard was supported by a grant from the French Federation of Cardiology.

Disclosures

None.

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KEY WORDS: antiplatelet therapy ■ atrial fibrillation ■ bleeding ■ percutaneous coronary intervention ■ triple therapy

Triple Antithrombotic Therapy in Atrial Fibrillation Patients With an Indication for Oral Anticoagulation Undergoing Percutaneous Coronary Intervention: A Case-Based Review of the Current Evidence

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Circ Cardiovasc Interv. 2015;8:
doi: 10.1161/CIRCINTERVENTIONS.115.003217
Circulation: Cardiovascular Interventions is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 1941-7640. Online ISSN: 1941-7632