Triple antithrombotic therapy for atrial fibrillation and coronary stents

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Triple therapy (TT) refers to the concurrent use of an oral anticoagulant (OAC), such as warfarin, and dual antiplatelet therapy (DAPT), such as acetylsalicylic acid (ASA) plus clopidogrel.[1] The most common clinical indication for TT is patients with atrial fibrillation (AF) who have acute coronary syndrome (ACS) or who have undergone percutaneous coronary intervention (PCI) with stent insertion, which accounts for approximately 5% to 8% of all patients who undergo PCI.[2] There is limited evidence to guide clinicians on prescribing TT. As such, it is difficult to estimate the benefit of TT over DAPT or dual therapy (ie, an OAC plus a single antiplatelet agent) in these patients. As expected, TT carries a higher risk of bleeding than dual therapy or DAPT do.[3] Further, the risk of bleeding increases with continued use.[4]

Owing to limited evidence and the complexity of this regimen, TT should only be prescribed after consultation with a cardiologist. Of note, the prescribing patterns of cardiologists for these patients might vary owing to the lack of definitive data. For example, a recent analysis of antithrombotic prescribing in patients with AF after PCI within one Canadian cardiology centre concluded that less than half of patients received TT and approximately one-fifth received non–evidence-based therapies.[5] The present article reviews the literature on TT, focusing on decisions regarding choice of anticoagulant or antiplatelet therapy and duration, and outlines how primary care prescribers can monitor TT, communicate the rationale for and duration of TT to patients, and reduce the risk of bleeding (**Box 1**).

Case description

Mrs L.F., an 80-year-old woman known to you, presents to your clinic with shortness of breath, fatigue, and a "racing heart," which started approximately 2 days ago. An electrocardiogram confirms AF with a heart rate of 120 beats/min. You review her chart to select an agent for AF stroke prevention and are reminded that she had a non-ST-segment elevation myocardial infarction 2 months ago, which was managed with 2 drug-eluting stents. She was prescribed 90 mg of ticagrelor twice daily for 12 months, 81 mg of ASA daily for life, 50 mg of metoprolol twice daily, 10 mg of ramipril daily, and 40 mg of atorvastatin daily. Her past medical history includes hypertension, type 2 diabetes mellitus, dyslipidemia, and osteoarthritis. Her other medications include 500 mg of metformin twice daily, 650 mg of acetaminophen twice daily, and 20 mg of paroxetine once daily, which was started during menopause for hot flashes. Mrs L.F. is a non-smoker and very rarely consumes alcohol. She has no mobility issues and lives independently in a condominium with her husband.

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Box 1. Practical tips for monitoring and communicating the rationale for and duration of antithrombotic TT to patients

When therapy is initiated, document the following in the patient's chart (paper or electronic medical record):

- indication for and intended duration of TT;
- the suggested target INR (eg, 2.0-2.5, 2.0-3.0) if warfarin is used;
- instructions for step-down therapy, along with duration of therapy;
- HAS-BLED score and reversible risk factors to address (review at each subsequent visit while taking TT); and
- the intended duration of proton pump inhibitor use, if taking for gastroprotection

Include the following on the prescription label:

- instructions for duration of TT (eg, "continue until [date], then stop")

Patient education:

- Emphasize the intended duration of TT and encourage the patient to report any bleeding
- Ensure the patient understands which antithrombotics are to be continued when TT is complete (especially with ASA, as it is available over the counter)
- Instruct the patient to avoid over-the-counter products that can increase the risk of bleeding (eg, NSAIDs, vitamin E, high-dose omega-3 [3-4 g/d], *G* natural health products [eg, ginkgo, ginseng, garlic])

ASA—acetylsalicylic acid; HAS-BLED—hypertension with a systolic blood pressure > 160 mm Hg, abnormal renal or liver function, stroke (caused by a bleed), bleeding, labile INR, elderly (age > 65 y), drugs (ASA, NSAIDs) or alcohol (≥ 8 drinks/wk); INR—international normalized ratio; NSAID—nonsteroidal anti-inflammatory drug; TT—triple therapy.

Mrs L.F.'s recent laboratory results revealed a hemoglobin A_{1c} level of 7.8% and a low-density lipoprotein cholesterol level of 2.6 mmol/L. Her complete blood count results, renal function, and liver enzyme levels were within normal limits. In the clinic today, her body mass index is 26 kg/m^2 and her blood pressure is 124/82 mm Hg. Her $CHADS_2$ (congestive heart failure, hypertension, age ≥75 y, diabetes mellitus, previous stroke or transient ischemic attack) score is 3. Her HAS-BLED (hypertension with a systolic blood pressure >160 mm Hg, abnormal renal or liver function, stroke [caused by a bleed], bleeding, labile international normalized ratio [INR], elderly [age >65 y], drugs [ASA, nonsteroidal anti-inflammatory drugs (NSAIDs)] or alcohol [≥8 drinks/wk]) score is 2, which is based on her age and ASA use. (This score does not take into account her other medications that increase her risk of bleeding [ie, ticagrelor and paroxetine]).

Mrs L.F. has an indication for an OAC for AF stroke prevention; however, you decide to consult her cardiologist, as she is currently taking DAPT for her recent ACS and coronary stents.

Bringing evidence to practice

Triple therapy might be prescribed for patients with concomitant AF and recent ACS, as DAPT has been shown to be superior to an OAC for reducing the risk of stent thrombosis,[6] but was inferior to an OAC for preventing thrombotic events in patients with AF.[7] The 2016 Canadian Cardiovascular Society (CCS) guidelines for the management of AF recommend TT (81 mg/d of ASA, 75 mg/d of clopidogrel, and an OAC) for 3 to 6 months in patients with AF who are 65 years of age and older, have a $CHADS_2$ score of 1 or more, and have undergone PCI, followed by clopidogrel plus an OAC for 6 to 9 months (12 months total) after the index event, and then OAC monotherapy.[1] However, this is a conditional recommendation based on low-quality evidence.[1] In place of TT, some cardiologists might choose DAPT for patients with a $CHADS_2$ score less than 2 or dual therapy (ie, clopidogrel plus an OAC) in patients with a high risk of bleeding.[1]

While there are several large randomized controlled trials (RCTs) evaluating antithrombotic regimens for ACS or AF alone, the available evidence for patients with concurrent ACS and AF is minimal, and is primarily based on observational studies and open-label RCTs (**Table 1**).[1,2,8-12] Meta-analyses have attempted to quantify the benefit of TT compared with other antithrombotic regimens; however, results are inconclusive owing to variance in the proportion of patients with ACS at baseline, lack of reporting of patient-specific risk factors (ie, $CHADS_2$ and HAS-BLED scores), various durations of TT, and poor study quality.[3,13,14] Conversely, the risk of bleeding with TT has been well quantified. Compared with DAPT or dual therapy, TT doubles the overall risk of bleeding and is associated with a 5% to 15% rate of major bleeding at 1 year.[3,9,15,16] Approximately 1 in 10 bleeds are fatal.[9,15] Not surprisingly, the rate of bleeding increases with increasing duration of TT.[4]

Two open-label RCTs[2,9] have compared TT to dual therapy in patients who underwent PCI (**Table 1**).[2,8-12] The WOEST (What is the Optimal Antiplatelet and Anticoagulant Therapy in Patients with Oral Anticoagulation and Coronary Stenting) trial compared warfarin plus clopidogrel with TT (ASA, warfarin, and clopidogrel) in 573 patients who received a coronary stent (69% had AF).[9] The PIONEER-AF-PCI (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 PCI) study, conducted with 2124 patients with AF who underwent PCI, had 3 treatment arms: dual therapy (low-dose rivaroxaban [15 mg/d] plus clopidogrel); TT with very low-dose rivaroxaban (2.5 mg twice daily); and TT with warfarin.[2] Neither study was powered to examine thrombotic events and thus differences in efficacy might not have been detected.[2,9] Both trials investigated any bleeding as the primary end point and concluded that dual therapy resulted in less bleeding than TT.[2,9] In the PIONEER-AF-PCI trial, a summary of which is available at **CFPlus**,* the primary end point was driven by bleeding requiring medical attention, and the difference in rate of major bleeding was not statistically significant between groups.[2] Further, only approximately 25% to 50% of patients had ACS as their index event.[2,9] Based on the WOEST study, the CCS guidelines recommend dual therapy (clopidogrel plus OAC) for 12 months in patients with AF who undergo *elective* PCI.[1]

Selection of anticoagulants for TT. Most of the limited evidence regarding TT is for warfarin. The aforementioned meta-analyses that assessed TT only included vitamin K antagonists—these studies provide the largest body of evidence (15 and 18 studies, N=7182 and N=17 708, respectively), although both are largely based on observational data.[3,13] If warfarin is used, consider an INR target of 2.0 to 2.5 and monitor INR frequently (eg, every 2 weeks), although this narrow target can be difficult to achieve.[1,17,18] The 2016 CCS AF guidelines suggest, based on extrapolation of data from the direct oral anticoagulant (DOAC) AF trials, using a DOAC, such as apixaban, dabigatran, or rivaroxaban, preferentially to warfarin for patients with nonvalvular AF and recent

*The **RxFiles newsletter** and **chart on Duration of Dual Antiplatelet Therapy and Triple Therapy for Cardiovascular and Cerebrovascular Indications** and **a summary of the PIONEER-AF-PCI trial** are available at **www.cfp.ca**. Go to the full text of this article online and click on the **CFPlus** tab.

Table 1. Summary of RCTs

STUDY	POPULATION	INTERVENTION OR COMPARATOR	OUTCOMES	COMMENTS
TT RCTs of patients who received a coronary stent				
PIONEER-AF-PCI,[2] 2016 • Open-label, randomized trial • 26 countries (about 10% from North America) • N = 2124	• Nonvalvular AF and PCI with stent • Mean age 70 y • Elective PCI: 61.5% • CHA_2DS_2-VASc score: 0-1, 9.5%; 2-4, 54.7%; 5-7, 35.9% • HAS-BLED score: ≤ 2, 29.8%; 3-4, 65.8%; ≥ 5, 4.5%	• Group 1: 15 mg/d of rivaroxaban (10 mg/d if CrCl 30-50 mL/min) and $P2Y_{12}$ inhibitor for 12 mo • Group 2: 2.5 mg of rivaroxaban twice daily and DAPT for 1, 6, or 12 mo; step down to rivaroxaban and ASA (75-100 mg/d) until 12 mo after stent • Group 3: warfarin (INR 2.0-3.0) and DAPT for 1, 6, or 12 mo; step down to warfarin and ASA (75-100 mg/d) until 12 mo after stent • $P2Y_{12}$ inhibitor: 94% clopidogrel • Proportion of patients taking 10 mg/d of rivaroxaban not reported	• Primary end point of clinically significant bleeding (composite of TIMI major and minor bleeding, and bleeding requiring medical attention): group 1, 16.8%; group 2, 18%; group 3, 26.7% • $P < .01$ for groups 1 and 2 vs group 3; NNT = 11 and NNT = 12, respectively, at 1 y • CV event (CV death, MI, or stroke): no difference	• DAPT duration for groups 2 and 3 (non-randomized): 1 mo, 15.8%; 6 mo, 34.9%; 12 mo, 49.3% • PPI use at baseline: 38% • Not powered to assess CV outcomes • Difference in major bleeding was not statistically significant between groups
ISAR-TRIPLE,[8] 2015 • Open-label, randomized trial • Germany and Denmark • N = 614	• Indication for long-term OAC and need for PCI • Mean age 73 y • > 65% stable angina • > 80% AF • DES: 100% • $CHADS_2$ score: 0-1, 17%-21%; 2-3, 61%-64%; 4-5, 13%-20%; > 5, 1%-2% • $CHADS_2$ score ≥ 3: 6 wk (22.4%) vs 6 mo (14.5%)	• TT (75 mg/d of clopidogrel, 75-200 mg/d of ASA, and warfarin [INR 2.0-3.0]) for 6 wk vs 6 mo	• Primary end point (composite of death, MI, stent thrombosis, stroke, and TIMI major bleeding): no difference at 9 mo	• No significant differences in secondary end points between groups, including TIMI major bleeding • No net clinical benefit between 6 mo vs 6 wk of TT
WOEST,[9] 2013 • Open-label, randomized trial • Netherlands • N = 571	• Indication for long-term OAC and need for PCI • Mean age 70 y • 69% AF • Only 27% had ACS at baseline • 65% DES, 30% BMS	• Dual therapy (75 mg/d of clopidogrel and warfarin) for 12 mo vs TT (80-100 mg/d of ASA, 75 mg/d of clopidogrel, and warfarin) for 12 mo • Target INR of 2.0-3.0 for both groups	• Primary end point (any bleeding at 1 y): 19.4% vs 44.4%, HR = 0.36, $P < .0001$, NNT = 4 • Secondary end point (composite of death, MI, stroke, target vessel revascularization, and stent thrombosis): 11.1% vs 17.6%, HR = 0.6, $P = .025$, NNT = 16, driven by reduction in death	• Duration –BMS: 1 mo to 1 y –DES: at least 1 y • No significant difference in TIMI major bleeding • Underpowered for ischemic events • PPI use at baseline: about one-third

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STUDY	POPULATION	INTERVENTION OR COMPARATOR	OUTCOMES	COMMENTS
TT trials with direct OACs for secondary ACS prevention*				
ATLAS ACS 2-TIMI 51,[10] 2012 • Randomized, double-blind phase 3 trial • 44 countries (5.5% from North America) • N = 15 526 • Missing data for 15.5% patients who prematurely discontinued the study; vital status not obtained for 1117 (7.2%) at the end of the trial	• Mean age 62 y • STEMI: 50% • NSTEMI: 25.6% • Unstable angina: 24% • 60% underwent revascularization	In addition to ASA plus clopidogrel or ticlopidine: • Placebo vs 2.5 or 5 mg of rivaroxaban twice daily Mean of 13 mo	• Primary end point (composite of CV death, MI, and stroke): placebo, 10.7%; 2.5-mg rivaroxaban, 9.1% (NNT = 63); 5-mg rivaroxaban, 8.8% (NNT = 53) • Compared with placebo, 2.5 mg of rivaroxaban (but not 5 mg) decreased CV events (4.1% vs 2.7%) and overall mortality (4.5% vs 2.9%) ($P < .05$ for both) • TIMI major bleeding not associated with CABG: placebo, 0.6%; 2.5-mg rivaroxaban, 1.8% (NNH = 84); 5-mg rivaroxaban, 2.4% (NNH = 56) • Fatal bleeding: not statistically significant	• In Canada, neither 2.5-mg nor 5-mg rivaroxaban tablets are commercially available, and 10-mg tablets are not scored
RE-DEEM,[11] 2011 • Randomized, double-blind phase 2 trial • 24 countries (5.4% from North America) • N = 1861	• Recent ACS • STEMI: 60% • NSTEMI: 40% • PCI: 55% • Mean age 61 y	In addition to ASA plus a $P2Y_{12}$ inhibitor: • Placebo vs 50, 75, 110, and 150 mg of dabigatran twice daily	• Primary end point (major [ISTH] or clinically relevant minor bleeding) at 6 mo: placebo, 2.2%; 50 mg, 3.5%; 75 mg, 4.3%; 110 mg, 7.9%; and 150 mg, 7.8%; $P < .001$ for linear trend • Ischemic CV events: not statistically significant (underpowered to assess)	• Addition of dabigatran to DAPT in post-MI patients was associated with a dose-dependent increase in major or clinically relevant minor bleeding • 110-mg and 150-mg dabigatran groups associated with a 4-fold higher risk of bleeding than placebo
APPRAISE-2,[12] 2011 • Randomized, double-blind trial • After enrolling 7392 patients, terminated prematurely owing to increased bleeding risk without reduction in ischemic events	• Recent ACS and ≥ 2 high-risk features • STEMI: 40% • NSTEMI: 42% • Unstable angina: 18% • PCI: 44% • Median age 67 y	In addition to ASA plus a $P2Y_{12}$ inhibitor: • 5 mg of apixaban twice daily (2.5 mg twice daily if CrCl < 40 mL/min) vs placebo Median 8 mo	• Primary end point (CV death, MI, or stroke): apixaban, 7.5% vs placebo, 7.9% ($P = .51$) • TIMI major bleeding: apixaban, 1.3% vs placebo, 0.5% (NNH = 125)	• Addition of apixaban to DAPT after ACS increased major bleeding risk without reducing ischemic events • PPI use at baseline: 24%

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Table 1 *continued from page 378*

ACS—acute coronary syndrome; AF—atrial fibrillation; APPRAISE-2—Apixaban for Prevention of Acute Ischemic Events 2; ASA—acetylsalicylic acid; ATLAS ACS#2–TIMI 51—Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome–Thrombolysis in Myocardial Infarction 51; BMS—bare-metal stent; CABG—coronary artery bypass graft; CHA_2DS_2-VASc—congestive heart failure, hypertension, age ≥ 75 y, diabetes mellitus, stroke or transient ischemic attack, vascular disease (previous MI, peripheral artery disease, or aortic plaque), age 65-74 y, sex category (ie, female); $CHADS_2$—congestive heart failure, hypertension, age ≥ 75 y, diabetes mellitus, and previous stroke or transient ischemic attack; CrCl—creatinine clearance; CV—cardiovascular; DAPT—dual antiplatelet therapy; DES—drug-eluting stent; HAS-BLED—hypertension with a systolic blood pressure > 160 mm Hg, abnormal renal or liver function, stroke (caused by a bleed), bleeding, labile INR, elderly (age > 65 y), drugs (ASA, NSAIDs) or alcohol (≥ 8 drinks/wk); HR—hazard ratio; INR—international normalized ratio; ISAR-TRIPLE—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; ISTH—International Society on Thrombosis and Hemostasis; MI—myocardial infarction; NNH—number needed to harm; NNT—number needed to treat; NSAID—nonsteroidal anti-inflammatory drug; NSTEMI—non-ST-segment elevation MI; OAC—oral anticoagulant; PCI—percutaneous coronary intervention; PIONEER-AF-PCI—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; PPI—proton pump inhibitor; RCT—randomized controlled trial; RE-DEEM—Randomised Dabigatran Etexilate Dose Finding Study in Patients with Acute Coronary Syndromes Post Index Event with Additional Risk Factors for Cardiovascular Complications Also Receiving Aspirin and Clopidogrel; STEMI—ST-segment elevation MI; TIMI—Thrombolysis in Myocardial Infarction; TT—triple therapy; WOEST—What is the Optimal Antiplatelet and Anticoagulant Therapy in Patients with Oral Anticoagulation and Coronary Stenting.
*Proportion of patients with AF not reported in the studies.

ACS.[1] However, the clinical efficacy and safety of DOACs in a TT regimen has not been established.

Of the DOACs, only rivaroxaban and dabigatran have randomized controlled *safety* data compared with warfarin (as part of TT) in patients with AF (**Table 1**).[2,8-12,19] However, these trials were not powered to evaluate *efficacy*, and therefore have not established a reduction in stroke and systemic embolism rates in AF. The PIONEER-AF-PCI study compared 15 mg of rivaroxaban daily plus 75 mg of clopidogrel daily, and 2.5 mg of rivaroxaban twice daily plus DAPT (75 mg/d of clopidogrel plus 75 to 100 mg/d of ASA), with warfarin plus DAPT (target INR of 2.0 to 3.0).[2] In terms of safety, both rivaroxaban strategies resulted in less clinically significant bleeding compared with warfarin (differences in major bleeding rates were not statistically significant).[2] At the time of publication, 2.5-mg tablets of rivaroxaban are not commercially available in Canada. As for dabigatran, a subgroup analysis of the RE-LY (Randomized Evaluation of Long-term Anticoagulation Therapy in Patients with Atrial Fibrillation and who are at Increased Risk of Stroke) trial evaluated the effect of DAPT with an OAC (dabigatran or warfarin) in preventing stroke and systemic embolism in a small proportion (4.9%) of patients with AF who were inadvertently taking a TT regimen at some point during the 2 years of follow-up.[19] There was limited detail regarding the duration of TT in these patients.[19] The addition of DAPT to an OAC increased major bleeding, but the absolute risk was lowest with 110 mg of dabigatran twice daily.[19] The other landmark AF trials that compared DOACs with warfarin excluded patients taking clopidogrel, and only approximately one-third of the patients were taking ASA.[20,21]

Three of the DOACs have been compared with placebo in TT regimens for secondary ACS prevention (**Table 1**)[2,8-12]; however, the proportion of patients with AF was not reported.[10-12] The RCTs involving dabigatran and apixaban failed to demonstrate a benefit, but revealed increased major bleeding rates.[11,12] The rivaroxaban trial used 2.5-mg tablets twice daily (not commercially available in Canada), which reduced the risk of cardiovascular events but increased the risk of major bleeding.[10]

Selection of antiplatelets for TT. Clopidogrel is the preferred antiplatelet to be used in combination with ASA and an OAC.[1] The newer, more potent antiplatelet agents, prasugrel and ticagrelor, are not recommended owing to an increased risk of bleeding compared with clopidogrel[22,23] and limited data on their role as part of TT.[1] However, if clopidogrel is not an option (eg, owing to allergy, stent thrombosis while receiving treatment), ticagrelor or prasugrel might be considered.[1] Aside from antiplatelet choice, low-dose ASA (81 mg/d) is recommended for patients receiving TT.[1]

Duration of TT. The duration of TT is highly individualized.* The CCS guidelines recommend 3 to 6 months of therapy, but note the duration is dependent on perceived risks of coronary stent thrombosis and major bleeding, such as the patient's HAS-BLED score, type of stent placed (bare metal vs drug eluting), and risk factors for stent thrombosis (eg, diabetes mellitus, first-generation drug-eluting stents, number of stents).[1]

Various durations of TT have been evaluated in RCTs.[2,8,9] The ISAR-TRIPLE (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) study compared 6 weeks with 6 months of TT and found no statistically significant difference between the groups for the primary composite end point of death, myocardial infarction, stent thrombosis, ischemic stroke, and major bleeding.[8] However, only one-third of the study population had recent ACS and 84% had AF (**Table 1**).[2,8-12] The primary end points for the WOEST and PIONEER-AF-PCI

trials were measured at 1 year; however, the duration of TT was at the discretion of the clinician.[2,9] Only 22% and 66% of patients enrolled in the PIONEER-AF-PCI and WOEST studies, respectively, received TT for 12 months. Once TT is complete, the patient should be stepped down to dual therapy (ie, an OAC plus an antiplatelet agent) for up to 12 months after stent insertion, followed by an OAC alone indefinitely.[1]

Communication among the cardiologist, primary care prescriber, and pharmacist is key to ensuring patients receive the appropriate regimen for the appropriate amount of time.

Reducing the risk of bleeding. The HAS-BLED score is a useful tool for assessing the risk of bleeding for patients with AF.[1] Addressing reversible risk factors is crucial in reducing bleeding risk, especially for patients taking TT. These risk factors include uncontrolled blood pressure, labile INR, use of medications that predispose the patient to bleeding (eg, NSAIDs, corticosteroids, selective serotonin reuptake inhibitors), and frequent alcohol consumption (ie, ≥8 alcoholic drinks per week). Patients taking TT should have their bleeding risk assessed before initiation and throughout treatment.

The addition of a proton pump inhibitor (PPI) should be considered as gastroprotection for patients taking TT, particularly for those with a history of gastrointestinal bleeding or ulcers.[1,16,17,24] While there is a lack of data addressing the efficacy of gastroprotection in TT, evidence does show that PPIs reduce the risk of upper gastrointestinal bleeding by at least 50% in patients taking DAPT.[25] Previously, concerns were raised regarding a potential drug-drug interaction between PPIs and clopidogrel based on observational trial data.[26] More recent RCT data suggest a clinically significant interaction is unlikely. However, if initiating a PPI in a patient taking clopidogrel, consider selecting an agent other than omeprazole or esomeprazole owing to a lower risk of drug interaction.[27] Once TT is complete, the PPI should be discontinued if it is no longer necessary.

Box 1 provides a list of practical suggestions for facilitating TT in practice.

Back to Mrs L.F.

Mrs L.F.'s cardiologist would like to see her in his office, but in the meantime, he asks you to stop her ticagrelor and initiate 75 mg of clopidogrel daily (starting in the morning after her last evening dose of ticagrelor) for 10 months (ie, she will receive a $P2Y_{12}$ inhibitor for a total of 12 months after coronary stent insertion). She is to continue taking her low-dose ASA for another month, then stop (ie, she will receive ASA therapy for a total of 3 months after coronary stent insertion). She is prescribed 3 mg of warfarin daily, with a suggested INR target of 2.0 to 2.5 while taking TT.

You decide to initiate 40 mg of pantoprazole daily while Mrs L.F. is receiving TT, and also decide to increase her metoprolol to 75 mg twice daily to achieve better rate control. You reassess her paroxetine, as selective serotonin reuptake inhibitors can increase the risk of gastrointestinal bleeding.[28] As she has not had any hot flashes in years, you decide to taper her paroxetine for eventual discontinuation. You also emphasize to her the importance of adhering to TT for the length of time prescribed, describe the signs and symptoms of bleeding, and recommend she avoid using any over-the-counter products that might increase her risk of bleeding (eg, NSAIDs, vitamin E, high-dose omega-3 [3 to 4 g/d], *G* natural health products such as ginkgo, ginseng, and garlic).

Conclusion

Questions remain regarding the ideal antithrombotic regimen and treatment duration for patients with AF who have ACS or who underwent PCI with coronary stenting. Balancing the risk of thrombotic events and bleeding is a therapeutic challenge. A cardiologist should be consulted before initiating and determining the duration of TT, with a clear plan for step-down to a dual- or single-agent regimen once TT is complete. As bleeding risk is cumulative, clear communication among health care providers, patients, and caregivers is important to facilitate adherence to the recommended duration of TT. Additionally, addressing any reversible risk factors for bleeding and considering gastroprotection are important steps to optimizing patient safety.

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