Antiplatelet, anticoagulant or both? A tool for pharmacists

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Introduction

Patients with atrial fibrillation (AF) are at an increased risk for thrombosis, and anticoagulant therapy, preferably with a direct oral anticoagulant (DOAC) for most patients, is indicated for prevention of such events.¹ In contrast, patients with acute coronary syndromes (ACSs) or atherosclerotic cerebrovascular accidents (CVAs) and those who have undergone percutaneous coronary intervention (PCI) have an indication for antiplatelet therapy for prevention of arterial ischemic events.² The risk/benefit of either antiplatelet or anticoagulant therapy alone is clearly defined in the literature.^{1,2} The dilemma is that the use of anticoagulation in AF has historically excluded patients with indications for dual antiplatelet therapy (DAPT), and landmark ACS trials have likewise excluded patients requiring concurrent anticoagulation.³⁻⁶ Therefore, in the common situation where patients have indications for both antiplatelet and anticoagulant therapy, what should you do? How do you weigh the evidence for efficacy and safety (bleeding)?

Both clotting factors and platelets interplay across all thrombotic situations, raising questions regarding the role of either reduced doses of DOACs or use of single antiplatelet therapy (SAPT) in situations where historic practice has been to use full-dose anticoagulants with DAPT therapy (triple therapy). The potential benefits and risks of adding anticoagulants in conditions such as ACS or stable coronary artery disease (CAD), traditionally managed with SAPT or DAPT, are also of interest. As such, our purpose is to provide an overview of the literature encompassing concomitant antiplatelet and DOAC therapy across a variety of indications

BOX 1 CHADS₂ score

CHADS ₂ score—sum of	Points
Congestive heart failure	1
Hypertension	1
Age ≥75 years	1
Diabetes mellitus	1
History of Stroke/transient ischemic attack	2

most likely to affect pharmacy practice and to provide front-line clinicians with practical information to assist with the management of care. A glossary of terms is available online at www.cpjournal (Appendix 1). Table 1 has been developed as a resource and covers the following clinical situations⁷⁻¹²:

- Among AF patients undergoing PCI, the use of standard or reduced-dose DOACs with antiplatelet therapy (Figure 1)
- Among patients post-ACS without atrial fibrillation, the use of standard or reduced-dose DOACs + DAPT
- Among patients with stable CAD without AF, the use of reduced-dose DOAC ± acetylsalicylic acid (ASA)

Patients with AF and PCI

Bottom Line: Based on lack of efficacy evidence, standard therapy (warfarin [international normalized ratio (INR) 2-3] + DAPT) is preferred for those at low risk of bleeding; however, the use of DOAC + SAPT is increasing in popularity

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BOX 2 CHA₂DS₂-VASc score

CHA ₂ DS ₂ -VASc score—sum of	Points
Congestive heart failure	1
Hypertension	1
Age ≥75 years	2
Diabetes mellitus	1
History of Stroke/transient ischemic attack	2
Vascular disease	1
Age >65 but <75 years	1
Sex category—female	1

due to the reported lower rates of major bleeding and ease of use across all patient populations.

Choices of regimens:

- With rivaroxaban, for those at moderate to high risk of bleeding, therapy is influenced by thrombotic risk: those having a greater stroke risk may be more appropriately managed with rivaroxaban 15 mg daily + P2Y₁₂ inhibitor. In contrast, patients with a lower CHADS₂ score but higher cardiovascular risk (i.e., multivessel disease, ACS, etc.) may be more appropriately managed with low-dose rivaroxaban 2.5 mg BID + DAPT.
- Apixaban 5 mg BID in combination with a P2Y₁₂ inhibitor may emerge as an option for those at moderate to high risk of bleeding. The utilization of standard AF doses of apixaban may provide clinicians with increased confidence from the perspective of mitigating stroke risk.

It is estimated that 5% to 8% of patients who undergo PCI have a concurrent diagnosis of AF.^{13,14} The AF-PCI scenario presents a true clinical quandary, as the clinician must assess the risk of cardioembolic stroke, done using the CHADS₂ score (Box 1) or CHA₂DS₂-VASc score (Box 2), as well as the risk of stent thrombosis and coronary events, which is more difficult to quantify. Therapy selection must also respect the risk of bleeding in light of multiple antithrombotic therapies prescribed.¹⁵ Patients with a high bleed risk will likely benefit more from reduced-dose regimens compared to their low-bleed-risk counterparts. The relative importance

assigned to the risk of bleeding is a balancing act dependent upon the consequences of a future thrombotic event for an individual patient—those anticipated to have devastating sequelae from a clot (e.g., death) have less value placed on bleeding risk and are apt to be managed aggressively with antithrombotic regimens. On this basis, the Canadian Cardiovascular Society (CCS) 2018 antiplatelet guidelines place greater value on thrombotic risk relative to bleeding risk and do not include bleeding risk in their treatment algorithms. Although the treatment guidelines favour DOACs over warfarin, they include triple-therapy regimens in certain situations.² The substantial bleed rates associated with traditional combination therapy (defined as triple therapy with warfarin + DAPT), however, have led to the investigation of strategies of reduced-intensity anticoagulation or SAPT with anticoagulation with a focus on bleed rates (Figure 1).

RE-DUAL PCI examined the use of dabigatran + SAPT.⁷ While it demonstrated a reduction in bleeding for both dabigatran + clopidogrel regimens relative to warfarin-based triple therapy, the trial design leaves clinicians with a level of uncertainty regarding the prevention of future events. Additionally, previous studies examining dabigatran have demonstrated a lack of protection for myocardial infarction, questioning the efficacy of dabigatran in a population at increased risk for future coronary events.³

Rivaroxaban has also been studied in this population in PIONEER AF PCI, which examined varying regimens of rivaroxaban with either SAPT or DAPT.⁸ For patients with a high CHADS₂ score, inferring a high stroke risk, clinicians may be more comfortable with rivaroxaban 15 mg daily + P2Y₁₂ inhibitor (note for patients with a creatinine clearance [CrCl] 30–50 mL/min, a dose-reduced rivaroxaban 10 mg daily + P2Y₁₂ inhibitor was used). In contrast, patients with a lower CHADS₂ score but higher cardiovascular risk (i.e., multivessel disease, ACS, etc.) may be more appropriately managed with low-dose rivaroxaban 2.5 mg BID + DAPT, due to the increased evidence for DAPT post-PCI and ACS.⁸ Despite the reduction in bleeding demonstrated with both rivaroxaban regimens compared to warfarin-based triple therapy, the limitations regarding available efficacy data require the clinician to assess first the patient's bleed risk or ability to be managed with warfarin and second their different thrombotic risks.

FIGURE 1 When atrial fibrillation (AF) and percutaneous coronary intervention (PCI) collide: Anticoagulant/antiplatelet combinations*

*None of these clinical trials were designed to assess efficacy outcomes.

Practices today tend to consist of a warfarin-based triple therapy regimen of shorter duration or the combination of rivaroxaban 15 mg daily + clopidogrel 75 mg daily in the vast majority of these patients. However, options with apixaban will emerge with the recently published AUGUSTUS trial.⁹ This trial was designed to address 2 different questions—comparing the use of apixaban (dosed as per the AF indication) in combination with clopidogrel to warfarin plus clopidogrel and examining both of these anticoagulation strategies with and without ASA. Ultimately, 4 combinations were addressed—apixaban with SAPT, apixaban with DAPT, warfarin with SAPT and warfarin with DAPT. The use of apixaban (as opposed to warfarin) resulted in a significant reduction in bleeding in

combination with SAPT or DAPT. The design of this trial allowed the investigators to determine that the removal of ASA (use of anticoagulation in combination with SAPT rather than DAPT) further decreased bleeding. So, within this trial, the use of apixaban and clopidogrel had the lowest bleeding rates and warfarin, clopidogrel and ASA the highest. This trial shares the limitations of other trials with respect to assessment of efficacy. Although the combined secondary endpoint of death or hospitalization favoured apixaban over warfarin, there was no difference detected for the combined endpoint of death or ischemic events, creating uncertainty as to the relevance of the hospitalization endpoint.

In Canada, the rivaroxaban 2.5 mg tablet has been approved for use only in stable CAD;

however, you may see it used in combination with DAPT, targeting the patient subgroup that has more value placed on cardiovascular risk/stent thrombosis. Apixaban, as dosed in the AUGUSTUS trial, is approved for use for AF; therefore, a regimen including apixaban at standard dosing for AF in combination with a P2Y₁₂ inhibitor is likely to be commonly used in the setting of AF with ACS/PCI, given bleeding was significantly reduced.

The CCS 2018 focused update on the use of antiplatelet therapy provides some additional considerations and recommends that the risks and benefits be balanced using clinical judgement.² Among this group of patients with AF undergoing PCI, risk stratification is also based on the urgency/findings of the PCI. Patients having PCI performed emergently due to an ACS or who have more problematic findings during the procedure are more likely to have a longer duration of antiplatelet therapy (6 months vs 3 months). In contrast, those having elective PCIs are more likely to have the antiplatelet regimen changed earlier (1 or 3 months). Regardless of the timing of the change in antiplatelet therapy, it is paramount that the pharmacist 1) ensure alteration of antiplatelet therapy at the decided time point and 2) ensure anticoagulant therapy for stroke prevention is adjusted, where applicable, to reflect applicable dosing for the indication of AF.

ACS without AF

Bottom Line: Standard therapy with DAPT is recommended but some patients at high thrombotic risk may be prescribed rivaroxaban 2.5 mg BID with DAPT.

Meta-analyses examining the use of ASA + warfarin in patients with recent ACS and no indication for anticoagulation therapy reported this combination as reducing thrombotic events compared to ASA alone. However, this benefit was largely outweighed by an increase in bleeding events.¹⁵⁻¹⁷ With DOACs showing similar or potentially lower major bleeding events in comparison to warfarin, new trials have reexamined combination therapy in an ACS population.^{10,11} These trials have been powered for efficacy compared to standard DAPT therapy and, as a result, are also able to appropriately assess bleed rates.

APPRAISE 2 and ATLAS ACS 2-TIMI 51 examined the addition of apixaban or rivaroxaban, respectively, to DAPT in the setting of

ACS.^{10,11} APPRAISE 2 was stopped early due to excess bleeding, and the apixaban regimen is not recommended for this reason.¹¹ ATLAS ACS 2-TIMI 51, studying 2 regimens of rivaroxaban, reported an increased risk of bleeding for minimal benefit among a population at low risk of bleeding (Table 1).¹⁰ Therefore, standard therapy with DAPT is recommended, but some patients at high thrombotic risk may be prescribed this additional therapy.

Stable CAD without AF

Bottom Line: ASA alone is recommended for most patients, with the combination of rivaroxaban 2.5 mg BID plus ASA reserved for patients at high thrombotic risk.

Even with medical therapy, patients with stable CAD continue to have a 5% to 10% risk of recurrent thrombotic events each year.¹⁸ Previous studies examining the use of warfarin with or without ASA to further reduce risk in stable CAD provided evidence of decreased events but with an increased risk of bleeding, including intracranial hemorrhage.¹⁹ The COMPASS trial studied rivaroxaban therapy 2.5 mg BID with ASA vs rivaroxaban 5 mg BID vs ASA alone and examined efficacy outcomes to assess the risk reduction of this additional therapy.¹² However, due to previous warfarin studies showing an unacceptable level of additional harm, it was also important to assess the risk of bleeding. The addition of rivaroxaban in the setting of stable CAD demonstrated benefit but with increased bleeding in a low bleed risk population. The additional bleeding events in a low-risk population make rivaroxaban 2.5 mg BID with ASA most appropriate for patients with a low baseline bleed risk who have a high risk of future thrombotic events (e.g., multiple vascular risk factors), including those whose only treatment option for CAD is maximal medical therapy as other interventions (e.g., stent placement or surgery) are not appropriate.

Role of the community pharmacist to improve patient outcomes

With the wide variety of anticoagulant/antiplatelet regimens, community pharmacists are well positioned to ensure appropriate management, given they are accessible (having patient encounters with refill prescriptions) and aware of all prescription therapies. Specific to combination antithrombotic therapies, there are

TABLE 1 Overview of key trials

Patients with nonvalvular AF undergoing PCI						
Bottom line: If low bleed risk, standard therapy with warfarin [INR 2-3] + DAPT If moderate to high bleed risk: a) Rivaroxaban Stroke risk > cardiovascular (stent thrombosis) risk, then rivaroxaban 15 mg daily with P2Y ₁₂ inhibitor Cardiovascular (stent thrombosis) risk > stroke risk, then rivaroxaban 2.5 mg BID with DAPT ¹² b) Apixaban: Apixaban 5 mg BID + clopidogrel c) Dabigatran: Dabigatran 150 mg BID + clopidogrel						
	Anticoagulant/ antiplatelet studied	Typical patient	Major bleeding vs warfarin regimen	Composite efficacy vs warfarin regimen	Duration of therapy	Summary
RE-DUAL PCI ⁷ (2017) N = 2725	Dabigatran 110 mg BID + clopidogrel vs dabigatran 150 mg BID + clopidogrel vs warfarin (INR 2-3) + DAPT	72-year-old white man with nonvalvular AF with a CHADS ₂ -VASc of 4 and moderate bleed risk (average HASBLED score of 3) who underwent PCI for ACS or stable angina	Dabigatran 110 mg BID + clopidogrel Decreased bleeds^a NNT = 9 Dabigatran 150 mg BID + clopidogrel Decreased bleeds^a NNT = 19	Dabigatran 110 mg BID + Clopidogrel Unknown, not powered for outcome^b Dabigatran 150 mg BID + clopidogrel Unknown, not powered for outcome^b	12.3 months	Dabigatran reduced major bleeding and CRNM bleeds, but it is unclear if these regimens have similar efficacy outcomes to triple therapy. Standard therapy (warfarin [INR 2-3] + DAPT is preferred)
PIONEER AF PCI ⁸ (2016) N = 2124	Rivaroxaban 15 mg daily + clopidogrel vs rivaroxaban 2.5 mg BID + DAPT vs warfarin (INR 2-3) + DAPT	71-year-old white man with nonvalvular AF with an average CHADS ₂ -VASc of 4-5 and a moderate bleed risk (average HASBLED of 3) who underwent PCI for ACS or stable angina	Rivaroxaban 15 mg daily + P2Y ₁₂ inhibitor Decreased bleeds^c NNT = 10 Rivaroxaban 2.5 mg BID + DAPT Decreased bleeds^c NNT = 13	Rivaroxaban 15 mg daily + P2Y ₁₂ inhibitor Unknown, not powered for outcome^d Rivaroxaban 2.5 mg BID + DAPT Unknown, not powered for outcome^d	1-12 months	Compared to warfarin + DAPT, both rivaroxaban regimens had less major bleeding, but it is unclear if these regimens have similar efficacy outcomes to warfarin-based triple therapy. Patients need to be individually risk stratified: No concerns regarding bleed risk: Warfarin (INR 2-3) + DAPT Patients at moderate to high bleed risk: If stroke risk supersedes risk of stent thrombosis, then rivaroxaban 15 mg daily + P2Y ₁₂ inhibitor If stent thrombosis risk supersedes risk of stroke, then rivaroxaban 2.5 mg BID + DAPT

(continued)

TABLE 1 (continued)

AUGUSTUS ⁹ (2019) N = 4614	Apixaban 5 mg BID + clopidogrel vs warfarin (INR 2-3) + clopidogrel	71-year-old white man with CHADS ₂ -VASc of 4 and moderate bleed risk (median HASBLED of 3) who underwent PCI for ACS or stable angina or medically managed for ACS	Apixaban 5 mg BID + clopidogrel Decreased bleeds^e NNT = 24	Apixaban 5 mg BID + clopidogrel Decreased but not powered for outcome ^f and no difference with defined ischemic endpoints ^g	6 months	Compared to warfarin, apixaban had less major and CRNM bleeding. Regardless of whether apixaban or warfarin was used, the inclusion of ASA increased bleeding. It is unknown if ischemic outcomes are similar, although apixaban decreased the secondary endpoint of death or hospitalization. No concerns regarding bleed risk: Warfarin (INR 2-3) + DAPT Patients at moderate to high bleed risk: Apixaban 5 mg BID + P2Y ₁₂ inhibitor
	Both of the above regimens with and without ASA		Inclusion of ASA with either regimen Increased bleeds^e NNH = 14	Use of ASA (vs placebo) showed no difference, but not powered for outcome ^g		
ACS (within 7 days of therapy initiation) without AF Background therapy with DAPT with randomization for the anticoagulant studied compared with placebo						
Bottom line: Standard therapy with DAPT is preferred; selected patients at high cardiovascular (stent thrombosis) risk may be prescribed rivaroxaban 2.5 mg BID + DAPT						
	Anticoagulant studied	Typical patient	Major bleeding vs placebo	Composite efficacy endpoint vs placebo	Duration of therapy	Summary
ATLAS ACS 2-TIMI 51 ¹⁰ (2012) N = 15,526	Rivaroxaban 2.5 mg BID vs rivaroxaban 5.0 mg BID vs placebo	62-year-old white man with a history of HTN and either DM or prior MI with low bleeding risk	Rivaroxaban 2.5 mg + DAPT Increased bleeds^c NNH = 84	Rivaroxaban 2.5 mg + DAPT Decreased events^d NNT = 63	13.1 months	While efficacy benefit with rivaroxaban occurred, it is offset in relation to increased bleeding; use of rivaroxaban + DAPT in this setting should be considered in a patient at low risk of bleeding. Standard therapy: DAPT is preferred
			Rivaroxaban 5 mg + DAPT Increased bleeds^c NNH = 56	Rivaroxaban 5 mg + DAPT Decreased events^d NNT = 53		
APPRAISE-2 ¹¹ (2011) N = 7392	Apixaban 5 mg BID vs placebo	67-year-old white man with a history of DM and HF and moderate bleed risk (including patients with a history of stroke, renal dysfunction)	Apixaban 5 mg BID Increased bleeds^c NNH = 125 (terminated early for harm)	Apixaban 5 mg BID Unknown, trial stopped early^d	11 months (anticipated 1.25 years)	Apixaban regimen is not recommended given increased bleeding. Standard therapy: DAPT is preferred

(continued)

TABLE 1 (continued)

Stable CAD without AF						
Bottom line: Standard therapy with ASA alone for most patients; rivaroxaban 2.5 mg BID with ASA is most appropriate for those with a high risk of thrombotic events that are at low risk of bleeding						
	Anticoagulant/ antiplatelet studied	Typical patient	Major bleeding vs ASA alone	Composite efficacy vs ASA alone	Duration of therapy	Summary
COMPASS ¹² (2017) N = 27,395	Rivaroxaban 2.5 mg BID + aspirin 100 mg daily vs rivaroxaban 5 mg BID vs aspirin 100 mg daily	68-year-old white man with stable CAD with hypertension and a previous MI on an ACEi, statin and B-blocker with low bleed risk	Rivaroxaban 2.5 mg twice daily + aspirin 100 mg daily Increased bleeds^e NNH = 84	Rivaroxaban 2.5 mg twice daily + aspirin 100 MG daily Decreased Events^d NNT = 144	23 months	Terminated early for benefit, may underestimate true bleed risk of therapy. While some benefit with the rivaroxaban + ASA occurred, this was offset by an increase in bleeding in a low bleed risk population. Use should be limited to those deemed appropriate for maximal medical therapy. Therapy of choice in most patients: ASA alone (standard therapy) Patients with high thrombotic risk: Rivaroxaban 2.5 mg twice daily + ASA
			Rivaroxaban 5 mg twice daily Increased bleeds^e NNH = 112	Rivaroxaban 5 mg twice daily No statistically significant difference^d		

ACEi, angiotensin-converting enzyme inhibitors; ACS, acute coronary syndrome; AF, atrial fibrillation; ASA, acetylsalicylic acid; BID, twice daily; CAD, coronary artery disease; CRNM, clinically relevant nonmajor; DAPT, dual antiplatelet therapy; DM, diabetes mellitus; HF, heart failure; HTN, hypertension; INR, international normalized ratio; PCI, percutaneous coronary intervention; MI, myocardial infarction; NNT, number needed to treat.

^aTIMI major or minor bleeding or bleeding requiring medical attention.

^bComposite endpoint of death, myocardial infarction, stroke or systemic embolism.

^cNon-coronary artery bypass grafting TIMI major bleeding.

^dComposite endpoint of death from cardiovascular causes, myocardial infarction and stroke.

^eISTH, International Society on Thrombosis and Haemostasis major bleeding or clinically relevant nonmajor bleeding.

^fDeath or hospitalization.

^gDeath or ischemic events (stroke, myocardial infarction, stent thrombosis [definite or probable] or urgent vascularization).

several important key patient counselling elements (Table 2). It is important that the indication for each component of therapy, as well as intended duration, be clearly identified at the initiation of therapy—if at the point of receiving a new prescription for an anticoagulant/antiplatelet combination uncertainty is expressed, clarification should occur with the prescriber. Reassessment of the appropriateness of this plan should occur at refill intervals through monitoring and updating medical conditions that may impact therapies, including but not limited to

major or minor bleeding, thrombotic events and changes to renal function. Routine assessment should include pharmacokinetic interactions for the P2Y₁₂ inhibitors, including but not limited to CYP 3A4 (i.e., some anticonvulsants, azole antifungals, etc.), P-glycoprotein inhibitors (i.e., cyclosporine), and other CYP 450 enzymes. In addition, pharmacodynamic interactions that may increase bleed risk should be considered, such as antiplatelet agents or nonsteroidal anti-inflammatory drugs previously prescribed or self-selected as over-the-counter products.

TABLE 2 Key patient counselling elements for combined antithrombotic therapies

<ul style="list-style-type: none"> • Indication/benefit of each component of therapy
<ul style="list-style-type: none"> • Duration of each component of therapy and timing of reassessment <ul style="list-style-type: none"> • Start date and stop date for each agent • Plan after completion of course of therapy for each agent <ul style="list-style-type: none"> • Other agents continue at the same dose • Other agents continue at a different dose • A different agent is resumed or added
<ul style="list-style-type: none"> • Need for reassessment of therapy by health care professional <ul style="list-style-type: none"> • Risk/benefit of therapy should be reassessed with occurrence of thrombotic events, bleeding, changes in other medical conditions/drug therapy • Periprocedural regimens
<ul style="list-style-type: none"> • Side effects <ul style="list-style-type: none"> • Increased bleeding risk of combination of antiplatelet/anticoagulant therapy • Patient strategies to identify and seek appropriate medical attention for major bleeds • Patient strategies for identification and management of minor bleeds • Importance of discussion of management options with appropriate (prescribing) health care professional if experiencing side effects prior to stopping therapy independently
<ul style="list-style-type: none"> • Adherence and potential barriers <ul style="list-style-type: none"> • Risk of lack of adherence/missed doses should be explained • Product availability issues (i.e., rivaroxaban 2.5 mg) • Coverage issues • Process for noncardiac procedure and continuation/resumption of therapy

BOX 3 Trial design and endpoints

- A larger number of patients are required to reliably detect smaller differences between groups or those endpoints occurring less frequently.
- Given that bleeding occurs more commonly than thrombosis among patients prescribed antithrombotic agents, trials designed to primarily assess bleeding (safety) do not have enough patients to assess thrombosis (efficacy):
 - For AF patients undergoing PCI, trials assessing anticoagulant/antiplatelet combinations are only able to make conclusions about bleeding (safety endpoint) and not about efficacy.
 - For the indication of ACS or stable CAD, trials examining the addition of chronic anticoagulation were designed to make conclusions about efficacy and safety.

BOX 4 Interpreting bleeding

- Comparing bleeding rates between trials is problematic given that trials used different bleeding definitions and enrolled patients with different baseline risks for bleeding.
- Major bleeds can be catastrophic, resulting in mortality, intensive care admissions or extended hospital stays. All trials included these bleeding events.
- Clinically relevant nonmajor bleeding (CRNMB) affects the quality of life for our patients and consists of emergency room treatment, physician intervention to stop bleeding or temporary or permanent discontinuation of antithrombotic therapy. Relative to major bleeding, CRNMB occurs more frequently. Importantly, not all trials measured this type of bleeding.

Patients need to be engaged in the management of these more complex regimens to ensure optimal care delivery. The pharmacist can play a central role in this process, with regular assessments at each refill and through appropriate follow-up with other health care providers.

Summary

With a plethora of new evidence emerging for antithrombotic therapies and the use of DOACs with antiplatelet therapy, the community

pharmacist will play an important role in ensuring safe and optimal use of these therapies. To do so, however, awareness of the various antithrombotic combinations and their unique evidence, indications and risks will be necessary to ensure seamless care. We have provided an up-to-date overview of available data and clinical considerations to aid community pharmacists in assessing these combination antithrombotic regimens in order to optimize the care for patients and ensure safe provision of therapy. ■

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