Antithrombotic Therapy in Patients With Atrial Fibrillation Undergoing Coronary Stenting
A North American Perspective: Executive Summary

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Abstract—The optimal regimen of the anticoagulant and antiplatelet therapies in patients with atrial fibrillation who have had a coronary stent is unclear.1,2 It is well recognized that “triple therapy” with aspirin, clopidogrel, and warfarin is associated with an increased risk of bleeding. National guidelines have not made specific recommendations, given the lack of adequate data. In choosing the best antithrombotic options for a patient, consideration needs to be given to the risks of stroke, stent thrombosis, and major bleeding. This executive summary describes these risks, provides specific recommendations concerning vascular access, stent choice, concomitant use of proton pump inhibitors, and the use and duration of triple therapy after stent placement, based on the risk assessment. (Circ Cardiovasc Interv. 2011;4:522-534.)

Key Words: atrial fibrillation ■ antithrombotic therapy ■ warfarin ■ triple therapy ■ stent

The optimal regimen of the anticoagulant and antiplatelet therapies in patients with atrial fibrillation (AF) who have had a coronary stent is unclear.1,2 It is estimated that 5–7% of patients undergoing percutaneous coronary interventions (PCI) have AF or other indications for chronic oral anticoagulant therapy.3–5 These patients pose a significant dilemma for the interventional cardiologist because the combination of oral anticoagulants with aspirin and clopidogrel (“triple therapy”) during follow-up has been reported to result in an increase in risk of major bleeding.6 Major bleeding is a serious complication that is associated with increased morbidity and mortality particularly when it occurs shortly after a stent procedure.7,8 In one study among patients on triple therapy with aspirin, clopidogrel, and warfarin, major bleeding occurred in 4.7%, and approximately 50% of these patients died within 6 months.9

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The American College of Cardiology/American Heart Association/European Society of Cardiology (ACC/AHA/ESC) guidelines have been cautious to recommend triple therapy (aspirin, clopidogrel, and oral anticoagulation) in patients with AF undergoing PCI due to the increased bleeding risk and limited information about the safety and efficacy of this treatment regimen.10 Currently, the use of triple therapy is classified as a class IIb recommendation (may be considered) with a level of evidence C (expert opinion).10,11 Recently, the ESC Working Group on Thrombosis published a consensus document on the management of these patients.12,13 The authors conducted a careful review of the available studies and made a number of specific recommendations that have been supported by the ESC guidelines for the management of AF.14 They tempered these recommendations since they were largely based on expert opinion. The current document provides a North American view of the issues and is the opinion of select experts in the United States and Canada. Because much of the background information has been previously published in the ESC consensus document, prior studies will not be extensively reviewed here. The focus of this report will be on those patients who are on oral anticoagulant therapy for the treatment of nonvalvular AF undergoing PCI. Because the data available for patients with
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The mechanisms of thrombus formation differ between that associated with AF and that of coronary artery disease and stent thrombosis. Plasma factors (ie, coagulation factors) are more important in the development of thromboembolic events during AF and cellular factors (ie, platelets) are more important in the pathophysiology of atherothrombotic events. Consequently, anticoagulant therapies are more beneficial for prevention of thromboembolism in patients with AF and antiplatelet agents are of greater benefit in the prevention of ischemic events, including stent thrombosis, in patients undergoing PCI. Although both anticoagulant and antiplatelet therapies can be termed “antithrombotic,” the indications and complications of these 2 different types of treatment differ. Patients with AF and risk factors for stroke who do not take anticoagulants are clearly at increased risk of stroke, and patients who undergo a PCI with stent placement who do not take DAPT are clearly at increased risk of stent thrombosis and other major adverse events. Therefore, patients with AF who also undergo PCI with placement of a coronary stent have a higher risk for both thromboembolic events and stent thrombosis if they are not on both anticoagulant and antiplatelet therapy.

The choice of antithrombotic medications for patients with AF undergoing PCI is dependent on the balance between the risk of stroke/emboli, recurrent ischemic events, stent thrombosis, and major bleeding. Three antithrombotic drug combinations have been used most in practice: triple therapy (oral anticoagulation and dual antiplatelet therapy with aspirin and clopidogrel), oral anticoagulation, and 1 antiplatelet agent (aspirin or clopidogrel), or rarely, DAPT alone without oral anticoagulants. Although there are wide variations in type and duration of therapy in practice, triple therapy is the most common treatment regimen in this setting. For example, in a subset of patients in the Can Rapid Risk Stratification of Unstable Angina Patients Suppress ADverse Outcomes with Early Implementation (CRUSADE) registry with AF who were taking warfarin at hospital admission and underwent coronary stenting (n = 1247), 60% were discharged on triple therapy, 31% on DAPT therapy, 3.2% on warfarin plus clopidogrel, and 2.5% on warfarin plus aspirin.

A survey of the Society for Cardiac Angiography and Interventions (SCAI) membership was conducted in January 2011 regarding patients with AF taking warfarin; more than 168 members replied. The results are shown in online-only Data Supplement Table I. In such patients receiving a bare-metal stent (BMS), the majority of interventionalists (86%) preferred to use triple therapy for 1 month followed by warfarin and aspirin. In patients receiving a drug-eluting stent (DES), a greater duration of triple therapy was preferred, with 47.4% recommending triple therapy for 6 months or longer. Other combinations were less commonly selected. These findings confirm the wide variability in practice and the lack of consensus regarding the best antithrombotic therapy for these patients.

Stroke/Embolic Risk

The benefit of oral anticoagulants in the prevention of stroke and systemic embolization is well established in patients who have at least 1 risk factor for these events. The CHADS2 score is commonly used to assess risk of stroke. The score and associated risk of stroke are shown in online-only Data Supplement Table I, A. The risk of stroke increases with increasing scores, rising from an adjusted rate of 1.9/100 person-years for a score of 0 to a risk of 12.5/100 person-years or more for a score of 5 to 6. Although the CHADS2 risk score is only modestly predictive for stroke/emboli (c-statistic, 0.6), many large trials have shown the higher the CHADS2 score the greater the absolute benefit of oral anticoagulation with warfarin. The CHA2DS2-VASc score takes into account the extent of vascular disease, intermediate age, and sex (online-only Data Supplement Table II, B). It has been shown to have better discrimination of stroke risk particularly in low-risk patients, where those with a score of 0 have a very low risk of stroke and can be treated with aspirin alone in the absence of stenting.
In patients without a prior thromboembolic event, the risk of stroke or systemic embolism is relatively constant over time: 1.4%/y on warfarin and 2.4%/y on aspirin and clopidogrel, as reported in the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events—W (ACTIVE-W) trial.18 In this study, the benefit of warfarin over aspirin and clopidogrel was only seen when the international normalized ratio (INR) was in the therapeutic range more than 58% of the time.26 Although there are no data available concerning the risk of stroke or systemic embolism with AF after a PCI, it is not likely that it is increased substantially beyond that seen with AF alone unless there has been a recent embolic or a new cardiovascular event, such as a ST-elevation–myocardial infarction (STEMI). This should translate into a low risk per month (estimated to be 0.2%) on DAPT alone for AF patients at intermediate or high risk of stroke, based on data from ACTIVE W trial.18

Stent Thrombosis
The incidence of stent thrombosis averages 1–2% over the first year but is greatest in the first month regardless of the type of stent used.27,28 The rate slowly declines to less than 0.1%/y after the first year for BMS and 0.4 to 0.6%/y after the first year for the first-generation DES. Stent thrombosis is associated with a mortality of 10–20% and a myocardial infarction (MI) rate of 30–70% in those with early or late stent thrombosis.29 In the first year, however, meta-analyses of randomized trials have not shown any difference in stent thrombosis between BMS and DES, with an incidence of 1.1% for DES versus 1.3% for BMS.30 The duration of DAPT, however, was shorter in these early studies and often only 1 month for BMS and less than 6 months for DES. Also, mortality is not different between stent types in randomized trials but has been reported to be lower for DES-treated patients in a meta-analysis of registry studies.31 This may be attributed to confounding due to selection bias or to the off-setting risks of higher stent thrombosis and lower restenosis rates with DES in patients with more complex disease.32

The greatest risk factor for stent thrombosis is premature discontinuation of DAPT, which is associated with a 5- to 36-fold risk increase in stent thrombosis.20,33,34 If discontinued before 6 months, the risk is increased 2.5- to 5-fold. There are conflicting results regarding the need for DAPT beyond 6 months, with some studies showing an increased risk and others not.20,35,36 Additional risk factors for stent thrombosis include incomplete stent apposition, significant proximal vessel disease, malignancy, postprocedure Thrombolysis In Myocardial Infarction (TIMI) flow <3, residual dissection, bifurcation stents, low ejection fraction, ACS, renal failure, diabetes mellitus, left anterior descending artery location.20,27,33 Stent thrombosis is also increased in “off label” indications and after primary angioplasty for STEMI.37,38

Current ACC/AHA guidelines recommend DAPT in patients with an STEMI for at least 1 year for BMS and DES and in patients with unstable angina or NSTEMI receiving a BMS, DAPT should be given for 1 month and preferably for 1 year.39,40 A number of studies in the 1990s demonstrated that the most effective antithrombotic regimen to prevent stent thrombosis was DAPT with aspirin and a thienopyridine.41 Ticlopidine, a first generation thienopyridine, was used in these studies. In the Stent Antithrombotic Regimen Study (STARS) trial, DAPT reduced the occurrence of death, target lesion revascularization, stent thrombosis, and recurrent MI at 30 days from 3.6% with aspirin alone and 2.7% for aspirin and warfarin to 0.5% for aspirin and ticlopidine.42 Because clopidogrel, a second-generation thienopyridine, has fewer adverse effects than ticlopidine, such as thrombotic thrombocytopenic purpura and severe neutropenia, it rapidly became the thienopyridine of choice.43,44

It is also recognized that 15–50% of patients do not have adequate platelet inhibition, based on ex vivo pharmacodynamic testing with standard dose clopidogrel, and these patients are at an increased risk for adverse events.45 Increasing the dose of clopidogrel can partially overcome clopidogrel resistance.46 In the Clopidogrel optimal loading dose Usage to Reduce recurrent EveNTs-Optimal ANitplatelet Strategy for interventionS (CURRENT-OASIS 7) trial, although cardiovascular events were not reduced with double dose clopidogrel in the overall ACS study population, a significant reduction in 30-day events was observed among patients undergoing PCI including a reduction in definite stent thrombosis by 46%.47,48 This reduction was, however, associated with an increase in major bleeding events. Other P2Y<sub>12</sub> receptor inhibitors, such as prasugrel and ticagrelor, which are characterized by more potent platelet inhibitory effects compared with clopidogrel, also significantly reduce stent thrombosis compared with clopidogrel with the incidence of definite or probable stent thrombosis decreasing by 52% and 25%, respectively, at 12 to 15 months.49,50 However, these more potent antiplatelet agents are associated with an increased risk of spontaneous bleeding. As such, prasugrel and ticagrelor should not to be used in combination with oral anticoagulants until adequate safety data are available.

Major Bleeding
One of the most important factors in choosing an antithrombotic regimen is the risk of major bleeding. Major bleeding has been associated with a 3- to 7-fold higher mortality among ACS patients compared with patients without bleeding.7,85 There are numerous definitions of bleeding, but the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) severe/life threatening bleeding and Thrombolysis in Myocardial Infarction (TIMI) major bleeding are most commonly used. Both have been associated with increased mortality.7,51,52 In a combined analysis of the Catheterization and Urgent Intervention Triage Strategy (ACUITY) and HORIZONS-AMI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) trials, TIMI major bleeding was most predictive of mortality within 1 year (hazard ratio [HR] = 4.45) among patients with ACS.51 Recently, the Bleeding Academic Research Consortium recommended a new classification of bleeding.53 They suggested to categorize bleeding into 5 different types ranging from mild to severe to provide a more uniform classification of bleeding and to better compare individual trials and drugs or interventions (online-only Data Supplement Table III).
The most devastating bleeding event is an intracranial hemorrhage. In some series, this accounted for 90% of the deaths from warfarin-associated hemorrhage in the first 30 days after initiation of therapy and accounted for the majority of disability among survivors.\(^5\) Prasugrel has been shown to cause more intracranial bleeding than clopidogrel in patients with prior cerebrovascular disease, and elevated mortality rates have been reported after intracranial hemorrhage among patients treated with ticagrelor.\(^49,50\)

Early bleeding risk in patients undergoing PCI can be estimated from clinical factors. In one study, non–coronary artery bypass graft–related bleeding in the first 30 days after PCI was predicted by 6 factors (age, sex, serum creatinine, white blood cell count, anemia, presentation with a STEMI or non-STEMI, and the type of antithrombotic medications).\(^51\) In these patients, the risk score predicted major bleeding from 1% in the lowest risk patients to 40% in the highest-risk patients.

Risk factors for bleeding from warfarin have also been identified. Lip et al used a previously derived bleeding risk score, HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (>65 years), Drugs/alcohol concomitantly), and applied it to patients with atrial fibrillation in the Stroke Prevention Using an ORal Thrombin Inhibitor in Atrial Fibrillation (SPORTIF) III and V trials.\(^55,56\) When compared with other scores, it performed modestly better (c-statistic, 0.67), with a graded risk from 1.2–9.5% over 1.5 years. Importantly, aspirin or nonsteroidal anti-inflammatory drugs increased the risk nearly 2-fold (HR = 1.98). The risk factors identified by multivariable analysis in this study were aspirin use, creatinine clearance <50 mL/min, age >75 years, diabetes, or left ventricular dysfunction. Tighter control of the INR with levels between 2 and 2.5 when on triple therapy has been shown to reduce bleeding complications without an increase in major adverse cardiac events compared with those who did not maintain an INR within this range.\(^3\) Genotype-guided therapy has been studied in patients receiving warfarin as a means of reducing bleeding and improving the average percentage time in the therapeutic range; however, to date, randomized trials have failed to demonstrate benefit.\(^57,58\)

Cumulative bleeding risk with both oral anticoagulants and antiplatelet agents increases in direct relation to the duration of treatment. In the ACTIVE W trial the risk of major hemorrhage was similar for oral anticoagulants (2.21%/y) and aspirin and clopidogrel (2.42%/y).\(^18\) Although the risk for bleeding on warfarin is greatest in the first month after initiation, it remains steady afterward. The bleeding risk for aspirin and clopidogrel in the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA) trial was greatest in the first month and declined over the next year.\(^59\) Patients who did not have a major bleeding episode in the first year had no increased bleeding with continued treatment compared to aspirin alone.\(^60\) This is in contrast with novel P2Y12 receptor inhibitors, which was associated with increased rates of spontaneous bleeding over time.\(^61\)

Not surprisingly, the risk of bleeding rises with an increased number of antithrombotic agents. In one study of 21,443 elderly patients followed on average for 22 months after an acute MI, bleeding was 1.7 times more frequent with DAPT and 1.9 times more frequent with aspirin plus warfarin when compared with aspirin monotherapy.\(^62\) Similarly, in a nationwide registry of 40,812 patients with acute MI in Denmark, the risk of bleeding was 2.6% for aspirin, 4.6% for clopidogrel, 4.3% for DAPT, 5.1% for aspirin plus an oral anticoagulant, 12.3% for clopidogrel plus an oral anticoagulant, and 12.0% for triple therapy over a mean follow-up of 16 months.\(^6\) The adjusted risk of bleeding (requiring hospitalization) was greatest among patients who had undergone PCI and received clopidogrel plus an oral anticoagulant (HR = 3.8) or were on triple therapy (HR = 3.3). Not all studies however have shown an increased bleeding risk on triple therapy.\(^63\) Several studies have shown that tight control of the INR between 2 to 2.5 can also reduce major bleeding risk to that seen with DAPT or warfarin and a single antiplatelet agent.\(^3,63\)

In a meta-analysis of available trials, the risk of major bleeding on triple therapy was estimated to be 2.2% at 1 month.\(^2\) This risk of major bleeding increases at 1 year to 4–12%, emphasizing that the longer the duration of triple therapy, the more the bleeding. Limiting the duration of triple therapy when possible should be considered as a key step to reducing overall bleeding risk.

**Recommendations**

**General Recommendations**

The general principle guiding the use of triple therapy is to choose a treatment strategy that is tailored to the individual patient, taking into consideration the anticipated risk of an adverse event particularly major bleeding. The following factors should also be considered.

**Vascular Access and Procedural Considerations**

Radial access has gained considerable interest and is being increasingly used as the preferred vascular access site given the reported lower risk of major bleeding. In a meta-analysis of available trials, major bleeding was reduced by 73% with a trend for reductions in death, MI, and stroke.\(^64\) The technique is more difficult to use and requires more training. It is also associated with a lower success rate in inexperienced hands and may increase radiation exposure.\(^65\) One randomized trial, the Radial versus Femoral Access for Coronary Intervention (RIVAL) trial, was recently reported.\(^66\) The study randomly assigned 7021 patients to radial or femoral artery access. The primary end point of death, MI, stroke, or non–CABG-related bleeding at 30 days was not different (3.7% versus 4.0%; HR, 0.92 [0.72–1.17]) between the respective access sites. Likewise, the secondary end point of death, MI, stroke, and the end point of non–CABG major bleeding were also not significantly different. However, major vascular complications were lower in the radial group (1.4% versus 3.7%, P < 0.0001), which was primarily due to fewer large hematomas. In 2 predefined subgroups, clinical centers with the most radial experience and patients with STEMI, the primary outcome was significantly better in the
radial group. At present, it would be reasonable to consider radial access in all patients who require chronic warfarin to reduce periprocedural bleeding risk and local access site complications. The choice of the procedural anticoagulant is important, with lower rates of bleeding reported with the use of bivalirudin and the use of femoral closure devices, and increased rates reported with the use of glycoprotein IIb/IIIa agents.67–70

**Indications for PCI and Stent Selection**

Careful consideration should be made to the necessity of PCI with stent placement because many stable angina patients can be managed on maximal medical therapy, thus avoiding the bleeding risks associated with triple therapy. When PCI is indicated, balloon angioplasty alone can at times achieve an acceptable result. In such patients, the risk of restenosis is higher, but when an acceptable or “stent-like” result occurs, thienopyridine may not be required resulting in a reduction in risk of bleeding that may outweigh the increased risk of restenosis.71

When stent placement is required during a PCI, and an oral anticoagulant is absolutely required long term, placement of a BMS is generally preferred over a DES. Because the risk of stent restenosis is greatest in long lesions, small vessels, and in patients with diabetes, the degree of benefit of a lower restenosis rate with DES in patients without these factors may be exceeded by the increased risk of bleeding with the longer duration of triple antithrombotic therapy.

In patients requiring PCI with long lesions, small vessels, diabetes, in-stent restenosis, or other risk factors for restenosis, placement of a DES is not unreasonable. Although the ACC/AHA guidelines recommend 12 months of DAPT, there are preliminary data indicating that stent thrombosis may be very low when DAPT is discontinued 6 or perhaps even 3 months after placement of a second-generation DES, such as the everolimus or zotarolimus-eluting stent.72,73 The randomized trial, Efficacy of Xience/Promus versus Cypher to Reduce Late Loss in Stent (EXCELLENT), compared 6 months versus 12 months of DAPT (and an everolimus versus sirolimus-eluting stent).74 The preliminary results were recently presented. The study showed that 6 months of DAPT was noninferior to 12 months for the primary end point of target vessel failure. In the subgroup with everolimus stent, the primary end point was noninferior with a shorter duration of DAPT, but this was not the case with the sirolimus stent. Based on emerging evidence that first-generation stents appear to have a greater late stent thrombosis rate, second-generation stents are preferred in patients who need a DES and triple therapy during follow-up.

**Proton Pump Inhibitor Use**

Because 20–30% of the major bleeding events after PCI are gastrointestinal (GI), the use of proton pump inhibitors (PPIs) has been advocated.75 Numerous studies have shown that these agents can reduce erosions, ulcers, and GI bleeding.76,77 However, pharmacodynamic and pharmacokinetic investigations have shown that certain PPIs reduce the ex vivo platelet inhibitory effects of clopidogrel, which have prompted a “boxed warning” by drug regulating authorities for the use of drugs interfering with CYP2C19 activity.78 It is important to note that this interaction is not class-specific but drug-specific, as it applies to only to PPIs (eg, omeprazole and esomeprazole) interfering with the activity of cytochrome P450 2C19 (CYP2C19), which is key in converting clopidogrel (prodrug) into its active metabolite. The clinical implications for such drug-drug interactions are controversial as results from retrospective registry data and post hoc assessments of randomized trials have produced conflicting findings. Post hoc analyses of prospective, randomized data suggest no clinically significant interaction between PPIs and clopidogrel.79 A recent meta-analysis also showed a modest increase in MI but not death.80 The COGENT (A Prospective, Randomized, Placebo-Controlled Trial of Omeprazole in Patients Receiving Aspirin and Clopidogrel Trial) trial, the only prospective randomized, double-blind comparison of omeprazole versus placebo in patients on aspirin and clopidogrel, showed reduced upper GI bleeding by more than 80% without a significant difference in cardiovascular outcomes.81 Although there was no apparent cardiovascular interaction between clopidogrel and omeprazole, the trial was not sufficiently powered and thus the results of COGENT cannot rule out a clinically meaningful difference in cardiovascular events due to use of a PPI. The benefit from the PPI may also come from reducing the GI site effects of aspirin; 2 prior placebo-controlled trials indicated that administering a PPI with aspirin reduces GI side effects, and in the CAPRIE trial, aspirin alone was more likely to result in hospitalization for GI bleeding as compared with clopidogrel alone.82–84 In the setting of dual antiplatelet therapy, GI bleeding is increased in those with a history of bleeding, peptic ulcer disease, advanced age, and use of anticoagulants, steroids, or NSAIDS.75 Although controversy remains concerning a reduction in the effectiveness of clopidogrel when on a PPI, these agents should be considered for the majority of patients on triple therapy especially if they are otherwise at increased risk of GI bleeding. PPIs not interfering with CYP2C19 activity and clopidogrel-mediated effects (eg, pantoprazole) should be considered in preference to those that are metabolized via CYP2C19 Available data suggest PPIs are superior to H2 receptor antagonists, although these agents may be a reasonable alternative in patients at lower risk for GI bleeding, and in those who do not require a PPI for refractory gastroesophageal reflux disease. Cimetidine can competitively inhibit CYP2C19, so other H2 receptor antagonists (eg, ranitidine) are a better choice in patients treated with clopidogrel.75

Given the benefit in reducing GI bleeding, routine prophylactic gastric acid–suppressing agents (not interfering with CYP2C19 activity) to patients receiving triple antithrombotic therapy should be considered.

**Warfarin and One Antiplatelet Agent**

The use of one antiplatelet agent in combination with warfarin is uncommon after PCI but is almost always prescribed after the initial use of triple therapy for 1 to 12 months. However, which antiplatelet agent, aspirin or clopidogrel, should be used is unclear. In practice, it appears that both antiplatelet agents are used but the combination of aspirin and warfarin is more common.6,21,85 However, the large CRUSADE...
registry showed that the use of either aspirin or clopidogrel in combination with warfarin occurred equally. There are scant data from observational studies to determine if there is better efficacy when clopidogrel is combined with warfarin than when aspirin is combined with warfarin. Because blockade of P2Y₁₂ receptor-mediated signaling with clopidogrel is associated with greater platelet inhibitory effects than COX-1 inhibition with aspirin, and the established role that P2Y₁₂ receptor blockade has on recurrent thrombotic events, clopidogrel might be expected to be more effective at reducing stent thrombosis but with increased bleeding. In the CAPRIE trial, 75 mg of clopidogrel as compared with 325 mg of aspirin without warfarin resulted in lower ischemic and bleeding events. One small observational study observed a lower incidence of stent thrombosis with clopidogrel plus warfarin as compared with aspirin plus warfarin. Although observational studies have shown an equal degree of bleeding with both regimens, one large national registry from Denmark with more than 82,854 patients has shown a 3-fold higher risk of major bleeding with warfarin plus clopidogrel as compared with warfarin plus aspirin. Until more data are available, it seems reasonable after a period of time on triple therapy to use either aspirin or clopidogrel when only 1 antiplatelet agent will be used.

The 2011 ACCF/AHA/HRS focused update of the AF guidelines and the 2010 ESC AF guidelines recommend treatment with warfarin alone after 12 months. Although the optimal duration of warfarin and one antiplatelet agent is not known, the increased risk of bleeding on this regimen supports this recommendation. In individual patients who are at high risk for thrombotic events or very late stent thrombosis or in patients who are at high risk for bleeding, it may be reasonable to use triple therapy for 1 month followed by one antiplatelet agent and warfarin thereafter. From the SCAI survey, this appears to be the most common strategy. When the risk of stent thrombosis is greater, longer durations of triple therapy may be needed. The optimal duration in this setting is not known but a general principle would be that the greater the risk of stent thrombosis, the longer the duration.

The most important factor concerning the duration of triple therapy is bleeding risk. Because the risk of stroke is small on DAPT therapy alone over 1 month, it is possible that patients with an intermediate CHADS₂ score (CHADS₂=2) might have an acceptable stroke risk while on DAPT alone for 1 month or longer if they have a high risk of bleeding on triple therapy. Because there are no data to support this strategy, it cannot be recommended at this time.

Finally, the 3 risks to be considered in selecting antithrombotic therapy (stroke/embolism, stent thrombosis, major bleeding) are not necessarily equal in terms of morbidity, mortality or quality of life. Many patients consider a large stroke to be a more devastating complication due to its impact on long-term disability, and thus should be weighted more heavily than stent thrombosis and bleeding when considering the balance of risk and benefit. The risk of death from each adverse event also varies but in general occurs among one-fourth to one-third of patients for each of the three major adverse events.

### Specific Recommendations

The following recommendations are based on the opinion of the authors considering the best available information. The authors recognize that several potential options are reasonable and that in individual patients, the optimal regimen will differ.

- Low-dose (≤100 mg) aspirin should be used. This is in agreement with the ACC/AHA guideline recommendations and the results of the recent CURRENT OASIS-7 trial.
- Gastric acid suppressing agents to reduce GI bleeding, preferably a PPI, should be given. If a PPI is used, an agent that interferes less with CYP2C19 activity and clopidogrel-mediated effects (eg, pantoprazole) should be preferred.
- Avoid concomitant nonsteroidal anti-inflammatory agent use.
- Clopidogrel is the thienopyridine of choice in combination with aspirin and warfarin. Prasugrel and ticagrelor cannot be recommended with warfarin until the safety of such triple therapy is demonstrated given the increased bleeding associated with these agents.
Warfarin should be dose adjusted and closely monitored to maintain the INR between 2 and 2.5.

Triple therapy use should depend on the balance of risks.

The authors used the following average crude estimates of risk for each adverse outcome listed below (low and high) to be:

- Stroke risk (CHADS<sub>2</sub>=1) on warfarin average 1.5%(1.0% for CHADS<sub>2</sub>=1–7% for CHADS<sub>2</sub>=5–6) per year (or adjusted stroke rates from 1.95%/y to >12.5%/y).
- Stent thrombosis (first year) on DAPT=1.5% (1–5%) but 5- to 36-fold higher for premature discontinuation within the first month, and 2.5- to 5-fold if between 1 and 6 months. On DAPT the risk is greatest in the first month.
- Major bleeding requiring hospitalization on triple therapy=6–15%/y; warfarin and 1 antiplatelet agent=6–12%/y; and on either DAPT or warfarin alone 2.5–4%/y. The rate is highest within the first 30 days after the procedure.

Based on these assumptions (Figure),

- Low stroke risk (CHADS<sub>2</sub>=0) and any stent thrombosis or bleeding risk: BMS: Dual antiplatelet therapy with aspirin and clopidogrel or prasugrel for 1 month and preferably for 12 months.
- DES: Dual antiplatelet therapy with aspirin and clopidogrel or prasugrel for 12 months or longer.
- Moderate/high stroke risk (CHADS<sub>2</sub> &gt;1), low stent thrombosis risk and low bleeding risk: BMS: Triple therapy for at least 1 month then oral anticoagulation (OAC)+single antiplatelet (AP) for 12 months.
- DES: Triple therapy for at least 6 months then OAC+single AP for 12 months.
- Moderate/high stroke risk and high stent thrombosis risk and low bleeding risk: BMS: Triple therapy for at least 1 month then oral anticoagulation (OAC)+single antiplatelet (AP) for 12 months.
- DES: Triple therapy for 12 months.
- Moderate/high stroke risk and any stent thrombosis risk and high bleeding risk: BMS: Triple therapy for at least 1 months then OAC+single AP for 12 months.
- DES: not recommended.
- Longer durations of dual antiplatelet therapy up to 12 months may be reasonable in patients undergoing stenting for STEMI and NSTEMI ACS and are at high risk of thrombotic events with a low risk of bleeding.
- After 12 months, warfarin alone should be given indefinitely. In patients at high risk for atherothrombotic events

**Figure.** Recommendations for the duration of triple therapy in patients with atrial fibrillation and a coronary stent (BMS or DES) with moderate/high stroke risk (CHADS<sub>2</sub> &gt;1). BMS indicates bare metal stent; DES, drug-eluting stent; OAC, warfarin; AP, antiplatelet agent; and triple therapy, aspirin, clopidogrel, and warfarin. *In patients at high risk for atherothrombotic events including stent thrombosis, continued single antiplatelet therapy with warfarin should be considered after 12 months.*

BMS= bare metal stent, DES= drug eluting stent

OAC= warfarin, AP= anti-platelet agent, Triple therapy= aspirin, clopidogrel and warfarin
including stent thrombosis, continued single antiplatelet therapy with warfarin should be considered after 12 months.

**Randomized Trials of Triple Therapy**

There are 3 registered ongoing randomized clinical trials of triple therapy in patients undergoing PCI. The Triple Therapy on Anticoagulation After Drug-Eluting Stent Implantation Trial (ISAR-TRIPLE) (NCT00776633) plans to enroll 600 patients and will compare a short course of triple therapy (6 weeks) with a long course (6 months) followed by aspirin and warfarin. The primary end point will be the composite of death, MI, definite stent thrombosis, stroke, or major bleeding 9 months. The What Is the Optimal Antiplatelet and Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary Stenting Trial (WOEST) (NCT00769938) will randomly assign 496 patients to either oral anticoagulation plus clopidogrel or to triple therapy. The primary end point will be any bleeding over 1 year. The Anticoagulation in Stent Intervention Trial (MUSICA-2) (NCT01141153) will randomly assign 304 patients with low to moderate stroke risk (CHADS2 ≤2) to DAPT or triple therapy. The primary end point will be death, MI, stroke, embolization, or stent thrombosis at 12 months. In addition, there are a number of on-going registries. These randomized trials should help to define some of the potential treatment options for these patients in the future, though the sample sizes are modest.

**New Drugs and Devices**

**Dabigatran and Other Newer Anticoagulants**

The Food and Drug Administration (FDA) recently approved dabigatran, an oral direct thrombin inhibitor that does not require laboratory monitoring of anticoagulation intensity, for the prevention of stroke and embolism in patients with AF based on the results of the 18 113 patient multicenter Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial. The study showed that a 150 mg dose dabigatran was superior to warfarin in the reduction of stroke and systemic embolism but was similar in rates of major hemorrhage, though a significantly lower intracranial bleeding rate. A lower dose (110 mg) had equal efficacy and less major bleeding than warfarin. In a recent analysis of the lower dose, age was an important factor with lower bleeding risks in those under 75 years and equal in those more than 75 years. Accordingly, a recent focused update on the management of patients with AF has implemented the results of RE-LY trial providing a class I recommendation with a level of evidence B for the use of dabigatran as a useful alternative to warfarin for the prevention of stroke and systemic thromboembolism in patients with paroxysmal to permanent AF and risk factors for stroke or systemic embolization who do not have a prosthetic heart valve or hemodynamically significant valve disease, severe renal failure (creatinine clearance <15 mL/min) or advanced liver disease (impaired baseline clotting function). The FDA approved a dose of 150 mg twice daily for patients with a creatinine clearance >30 mL/min and a dose of 75 mg twice daily for patients with severe renal insufficiency (creatinine clearance 15–30 mL/min). There are no dosing recommendations for patients with creatinine clearance <15 mL/min or patients on dialysis. The 110 mg twice-daily dose used in the RE-LY trial did not receive FDA approval. However, there are no studies that have been done using dabigatran in combination with aspirin and clopidogrel. Combinations of dabigatran and aspirin have been assessed in the Prevention of Embolic and Thrombotic Events with Persistent AF (PETRO) study. Any bleeding was significantly greater at the 150 mg dose than the 50 mg dose, averaging 18% but there were no major bleeding events, and aspirin did not seem to affect bleeding risk. In the RE-LY study, the use of aspirin with both doses of dabigatran increased major bleeding. This agent would be an attractive alternative to warfarin (as part of triple therapy), particularly used at a lower dose since it appears to have less bleeding in younger patients without loss of efficacy. In the RELY trial the small subset of patients on triple therapy with dabigatran did not appear to have less bleeding than those on triple therapy with warfarin. However, no firm recommendations can be made at this time concerning triple therapy with dabigatran, given the absence of safety and efficacy data in patients undergoing PCI. Given the lack of data to suggest harm, it is not unreasonable to use dabigatran in place of warfarin.

Oral direct factor Xa inhibitors, rivaroxaban and apixaban, are also being investigated for the treatment of patients with AF, although these have not been approved for this indication. Rivaroxaban was recently studied in the 14 000-patient multicenter randomized ROCKET-AF (Randomized, Double-Blind Study Comparing Once Daily Oral Rivaroxaban With Adjusted-Dose Oral Warfarin for the Prevention of Stroke in Subjects With Non-Valvular Atrial Fibrillation) trial. The preliminary results were presented at the AHA scientific sessions 2010. The results showed that the study group was a higher risk group compared with the RE-LY population, presenting with at least 2 or 3 risk factors for stroke. Rivaroxaban (20 mg once daily or 15 mg in patients with moderate renal impairment at screening) resulted in a 21% reduction in stroke or embolism compared with dose-adjusted warfarin in the on treatment analysis with an equivalent bleeding risk but with less fatal bleeding events and intracranial hemorrhage. This agent also is an attractive alternative to warfarin, but no data exist concerning its use with antiplatelet agents in patients with AF.

Apixaban in the dose-finding APPRAISE-1 trial showed a trend toward a reduction in ischemic events in patients with ACS but also demonstrated an increased bleeding risk particularly in those taking dual antiplatelet therapy. The larger phase 3 trial in patients with ACS, the APPRAISE-2 trial (NCT00831441) was stopped prematurely after enrollment of 7500 patients due to a significant increase in severe bleeding. In the AVERROES (Apixaban versus Acetylsalicylic Acid to Prevent Strokes) trial, patients (n = 5599) with AF for whom vitamin K antagonist therapy was unsuitable, apixaban (at a dose of 5 mg twice daily), reduced the risk of stroke or systemic embolism at 1 year without significantly increasing the risk of major bleeding or intracranial hemorrhage compared with aspirin. The ARISTOTLE trial (NCT00412984) has randomly assigned more than 18 000 patients with nonvalvular AF to dose-adjusted warfarin or 5 mg twice daily.
of apixaban and will be completed in the near future. The increased bleeding seen with this agent to date, however, raises concerns particularly in patients who need additional antiplatelet agents.

New Stent Designs/Technologies

The development of newer-generation DES has been largely due to the desire to reduce the incidence of late stent thrombosis and obviate the need for prolonged DAPT. The evidence available suggests that these newer stents may have a lower risk of stent thrombosis and thus shorter durations of DAPT may be possible. The results of a pooled analysis of the SPIRIT (A Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System in the Treatment of Subjects With De Novo Native Coronary Artery Lesions) trials comparing everolimus-eluting stent to the paclitaxel-eluting stent showed a trend toward lower definite or probable stent thrombosis (1.2% versus 1.9%). Likewise, the other second-generation DES, the zotarolimus-eluting stent also showed a trend toward reduced definite/probable stent thrombosis compared with a paclitaxel-eluting stent (1.1% versus 1.7%) but did have a lower rate of very late stent thrombosis after 1 year. The third-generation stents are being designed to further reduce stent thrombosis by using a biodegradable polymer coating on the stent or no polymer, abluminal drug delivery, and thinner struts. The most exciting advance is the development of the biodegradable stent. The initial results of the everolimus bioabsorbable BVS stent in 30 patients in the ABSORB (A bioabsorbable everolimus-eluting coronary stent system) study showed no stent thrombosis at 2 years with only 6 months of DAPT. ABSORB cohort B using an improved stent design was recently presented at the ACC Scientific Session 2011. In this analysis with 101 patients enrolled and at 9 months, there were no stent thrombosis events with 6 months of dual antiplatelet therapy. Compared with 227 similar patients from the SPIRIT trials using an everolimus stent, the MACE rates were similar. Based on these trials, the BVS stent was approved in Europe in January of 2011. If stent thrombosis can be minimized and DAPT can be reduced further then the issues discussed above concerning triple therapy will be greatly reduced.

Conclusions

This document provides a guide to clinicians faced with the difficult decision of when and how long to administer triple antithrombotic therapy to a patient with AF who has undergone a coronary stent placement. The recommendations are largely based on expert opinion rather than strong registry and randomized trial data. These recommendations are based on the estimation of the risk of stroke, stent thrombosis, and major bleeding and are meant to be a guide to assist in the assessment of individual patients. A number of randomized trials are ongoing or are planned, and until the trial results are known, sound clinical judgment is necessary to optimally treat such patients.

Disclosures

Dr Faxon has served on the Advisory Board for Boston Scientific and Sanofi-Aventis. Dr Moliterno has served as consultant to Boston Scientific and Merck-Schering-Plough. Dr Bhatt has received research grants from AstraZeneca, Bristol-Myers Squibb, Eisai, Sanofi-Aventis, and The Medicines Company. Dr Eikelboom has received consulting fees and/or honoraria from Astra-Zeneca, Boehringer-Ingelehm, Bristol-Myers-Squibb, Corgenix, Daiichi-Sankyo, Eisai, Eli-Lilly, Glaxo-Smith-Kline, Hemoscope, McNeil, Sanofi-Aventis, and grants and/or in-kind support from Accumetrics, AspirinWorks, Bayer, Boehringer-Ingelehm, Bristol-Myers-Squibb, Corgenix, Dade-Behring, Glaxo-Smith-Kline, and Sanofi-Aventis. Dr Angiolillo has received honoraria/lectures from Bristol Myers Squibb/Sanofi-Aventis, Eli Lilly Co, Daiichi Sankyo, Inc, and honoraria/advisory board from Bristol Myers Squibb/Sanofi-Aventis, Eli Lilly Co/Daiichi Sankyo, Inc, Astra Zeneca, The Medicines Company, Portola, Novartis, Medicure, Accumetrics, Arena Pharmaceuticals, Merck, Evolva, and investigator initiated research grants/awards from Bristol Myers Squibb/Sanofi-Aventis, GlaxoSmithKline (2007–2009), Otsuka (2008), Boston Scientific (2011) as well as sponsored research (Clinical Trial site) from Eli Lilly Co, Daiichi Sankyo, Inc, The Medicines Company, Portola, Accumetrics, Schering-Plough, Astra-Zeneca, Eisai, and Johnson and Johnson. Dr Berger has served as consultant to AstraZeneca, Boehringer Ingelheim, Eli Lilly/Daiichi-Sankyo, Medicure, Accu-metrics, and Ortho McNeil and has received research grants from Thrombovision, Helena, Accumetrics, AstraZeneca, Hemoscope, The Medicines Company, and Corgenix/Aspirinworks. He owns equity in Lumen Inc.

References

Antithrombotic Therapy in AF and Coronary Stenting


Antithrombotic Therapy in Patients With Atrial Fibrillation Undergoing Coronary Stenting: A North American Perspective: Executive Summary

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Supplemental Material

Supplemental Table 1. SCAI survey (168 respondents, conducted on 2/21/2011)

1. How often do you use a drug eluting stent in patients with AF on warfarin
   a. Never 1.8%
   b. Rarely 32.9%
   c. Sometimes 35.3%
   d. Often 30.6%

2. What is your preferred regimen in a patient with chronic AF on warfarin and requiring a DES?
   a. ASA, clopidogrel and warfarin for one month then ASA + warfarin 5.3%
   b. ASA, clopidogrel and warfarin for one month then clopidogrel + warfarin 19.3%
   c. ASA, clopidogrel and warfarin for 6 months or more 47.5%
   d. ASA and clopidogrel for 6 months or more 8.8%
   e. Clopidogrel and warfarin for 6 months or more 9.6%

3. What is your preferred regimen in a patient with chronic AF on warfarin and requiring a BMS?
   a. ASA, clopidogrel and warfarin for one month then ASA + warfarin 86.5%
   b. ASA, clopidogrel and warfarin for one month then clopidogrel + warfarin 7.6%
   c. ASA, clopidogrel and warfarin for 6 months or more 3.2%
   d. ASA and clopidogrel for 6 months or more 1.3%
   e. Clopidogrel and warfarin for 6 months or more 0.6%
Supplemental Table 2. Stroke Risk in Patients With Non-valvular AF Not Treated With Anticoagulation

a. CHADS\textsubscript{2} Risk Criteria Score

<table>
<thead>
<tr>
<th>CHADS\textsubscript{2} Risk Criteria Score</th>
<th>Patients (N)</th>
<th>Adjusted Stroke Rate (%/y)* (95% CI)</th>
<th>CHADS\textsubscript{2} Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior stroke or TIA</td>
<td>120</td>
<td>1.9 (1.2-3.0)</td>
<td>0</td>
</tr>
<tr>
<td>Age(\geq)75 years</td>
<td>463</td>
<td>2.8 (2.0-3.8)</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>523</td>
<td>4.0 (3.1-5.1)</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>337</td>
<td>5.9 (4.6-7.3)</td>
<td>3</td>
</tr>
<tr>
<td>Heart failure</td>
<td>220</td>
<td>8.5 (6.3-11.1)</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>65</td>
<td>12.5 (8.2-17.5)</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>18.2 (10.5-27.4)</td>
<td>6</td>
</tr>
</tbody>
</table>

*The adjusted stroke rate was derived from multivariate analysis assuming no aspirin usage.


AF indicates atrial fibrillation; CHADS\textsubscript{2}, Cardiac Failure, Hypertension, Age, Diabetes, and Stroke (Doubled); CI, confidence interval; and TIA, transient ischemic attack.

b. CHA2DS2-VASc

<table>
<thead>
<tr>
<th>CHA2DS2-VASc</th>
<th>Score</th>
<th>Score</th>
<th>Adjusted Stroke Rate (%/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure/LV dysfunction</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
<td>1</td>
<td>0.7</td>
</tr>
<tr>
<td>Age ≥75 years</td>
<td>2</td>
<td>2</td>
<td>1.9</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
<td>3</td>
<td>4.7</td>
</tr>
<tr>
<td>Stroke/TIA/TE</td>
<td>2</td>
<td>4</td>
<td>2.3</td>
</tr>
<tr>
<td>Vascular disease (prior MI, PAD, or aortic plaque)</td>
<td>1</td>
<td>5</td>
<td>3.9</td>
</tr>
<tr>
<td>Age 65-74 years</td>
<td>1</td>
<td>6</td>
<td>4.5</td>
</tr>
<tr>
<td>Female sex</td>
<td>1</td>
<td>7</td>
<td>10.1</td>
</tr>
<tr>
<td>Max=9</td>
<td>8</td>
<td>14.2</td>
<td></td>
</tr>
</tbody>
</table>

Supplemental Table 3. BARC definitions of bleeding

Type 0 No Bleeding

Type 1 Bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a health care professional. May include episodes leading to self-discontinuation of medical therapy by the patient, without consulting a health care professional.

Type 2 Any overt, actionable sign of hemorrhage (e.g. more bleeding than would be expected for a clinical circumstance; including bleeding found by imaging alone) that does not fit the criteria for Types 3, 4, or 5, but does meet at least one of the following criteria: 1) Requiring non-surgical, medical intervention by a health care professional 2) Leading to hospitalization or increased level of care 3) Prompting evaluation

Type 3
Type 3a
- Overt bleeding plus hemoglobin drop of 3 to <5 **g/dL (provided hemoglobin drop is related to bleed)
- Any transfusion with overt bleeding

Type 3b
- Overt bleeding plus hemoglobin drop ≥ 5 **g/dL (provided hemoglobin drop is related to bleed)
- Cardiac tamponade
- Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid)
- Bleeding requiring intravenous vasoactive agents

Type 3c
- Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation; does include intraspinal).
  - Subcategories; Confirmed by autopsy or imaging or LP
- Intra-ocular bleed compromising vision

Type 4 - CABG–related bleeding
- Perioperative intracranial bleeding within 48 hrs
- Reoperation following closure of sternotomy for the purpose of controlling bleeding
- Transfusion of ≥ 5 units of whole blood or packed red blood cells within a 48 period*.
- Chest tube output ≥ 2L within a 24 hour period
- If a CABG - related bleed is not adjudicated as at least a Type 3 severity event, it will be classified as ‘not a bleeding event’
• If a bleeding event occurs with a clear temporal relationship to CABG (i.e. within a 48 hour timeframe) but does not meet Type 4 severity criteria, it will be classified as ‘not a bleeding event’.

Type 5 - Fatal Bleeding
Type 5a
• Probable fatal bleeding: no autopsy or imaging confirmation, but clinically suspicious
Type 5b
• Definite fatal bleeding: overt bleeding or autopsy or imaging confirmation

Obs: Platelet transfusions should be recorded and reported, but are not included in these definitions until further information is obtained about the relationship to outcomes. * Cell saver products will not be counted. **Corrected for transfusion (1 unit PRBC or 1 unit whole blood = 1g/dL Hgb)

Supplemental Table 4. Bleeding scores

a. HAS-BLED bleeding score

<table>
<thead>
<tr>
<th>Letter</th>
<th>Clinical Characteristic</th>
<th>Score</th>
<th>HAS-BLED Score</th>
<th>Bleeds/100 patient-years</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>Hypertension</td>
<td>1</td>
<td>0</td>
<td>1.13</td>
</tr>
<tr>
<td>A</td>
<td>Abnormal renal and liver function (1 point each)</td>
<td>1 or 2</td>
<td>1</td>
<td>1.02</td>
</tr>
<tr>
<td>S</td>
<td>Stroke</td>
<td>1</td>
<td>2</td>
<td>1.88</td>
</tr>
<tr>
<td>B</td>
<td>Bleeding</td>
<td>1</td>
<td>3</td>
<td>3.74</td>
</tr>
<tr>
<td>L</td>
<td>Labile INRs</td>
<td>1</td>
<td>4</td>
<td>8.70</td>
</tr>
<tr>
<td>E</td>
<td>Elderly</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>Drugs or alcohol (1 each)</td>
<td>1 or 2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*“Hypertension” is defined as systolic blood pressure \(_{\text{160}}\) mm Hg. “Abnormal kidney function” is defined as the presence of chronic dialysis or renal transplantation or serum creatinine \(_{\text{200}}\) mol/L. “Abnormal liver function: is defined as chronic hepatic disease (e.g., cirrhosis) or biochemical evidence of significant hepatic derangement (e.g., bilirubin \(_{\text{3}}\) upper limit of normal, in association with aspartate transaminase/alanine transaminase/alkaline phosphatase \(_{\text{3}}\) upper limit normal). “Bleeding” refers to previous bleeding history or predisposition to bleeding (e.g., bleeding diathesis, anemia). “Labile INRs” refers to unstable/high international normalized ratios or poor time in therapeutic range (e.g., \(_{\text{60}}\)%). Drugs/alcohol use refers to concomitant use of drugs, such as antiplatelet agents and nonsteroidal anti-inflammatory drugs.*

page 113 Table 3