Case presentation: A 76-year-old man with rate-controlled atrial fibrillation (AF), diabetes mellitus, and prior stroke who is receiving warfarin to prevent recurrent stroke presents to the emergency department with chest pain, elevated serum troponin, and an ECG that demonstrates ST depression in the precordial leads. Cardiac catheterization reveals an ulcerated plaque and partially obstructive thrombus in the left circumflex coronary artery. Percutaneous coronary intervention is performed with placement of 2 bare-metal stents. What is the optimal antithrombotic therapy? What is the optimal antithrombotic therapy if the patient receives drug-eluting stents instead of bare-metal stents?

Efficacy of Antithrombotic Therapy in Patients With AF

Meta-analyses of randomized controlled trials in patients with nonvalvular AF indicate that oral vitamin K antagonist (VKA) therapy reduces the risk of stroke or systemic embolism by 42% compared with dual-antiplatelet therapy with the combination of aspirin and clopidogrel, whereas dual-antiplatelet therapy reduced the risk by 28% compared with aspirin alone. Recently, the RE-LY trial (Randomized Evaluation of Long-term anticoagulant therapy) showed that compared with warfarin the oral direct thrombin inhibitor, dabigatran etexilate given at a dose of 150 mg twice daily reduces stroke with less intracranial bleeding, and dabigatran 110 mg twice daily has similar efficacy with less bleeding. Dabigatran etexilate is not yet approved for stroke prevention in AF.

The 2006 American College of Cardiology/American Heart Association/European Society of Cardiology and the 2008 American College of Chest Physicians guidelines both recommend stratification of patients with AF according to their risk of stroke to guide the choice of antithrombotic therapy. The guidelines recommend VKA therapy for patients with a CHADS2 score >1, either aspirin or VKA therapy for patients with a CHADS2 score of 1 (with the American College of Chest Physicians giving preference to VKA), and aspirin for patients with a CHADS2 score of 0.

Efficacy of Antithrombotic Therapy in Patients With Coronary Artery Stents

In patients undergoing percutaneous coronary intervention with stent insertion, dual-antiplatelet therapy reduces the risk of cardiovascular death or myocardial infarction compared with aspirin alone or aspirin plus warfarin. Concerns about the risk of stent thrombosis prompted the American College of Cardiology/American Heart Association/Society for Cardiovascular Angiography and Interventions to recommend dual-antiplatelet therapy for a minimum of 1 month and ideally for 1 year in patients with a bare-metal stent and for a minimum of 1 year in those with a drug-eluting stent. For patients at high risk of bleeding, the guidelines recommend dual-antiplatelet therapy for a minimum of 2 weeks in those with a bare-metal stent. Under circumstances that prevent the use of clopidogrel for 1 year, the duration of dual-antiplatelet therapy studied for...
Food and Drug Administration approval was 3 months for sirolimus-eluting stents and 6 months for paclitaxel-eluting stents.9

The antithrombotic management of patients with AF receiving warfarin who undergo percutaneous coronary intervention with stent insertion requires clinicians to weigh the risk of thromboembolism against the risk of bleeding. Possible approaches include “triple therapy” using a VKA in combination with dual-antiplatelet therapy or dual-antiplatelet therapy alone.

Efficacy of Triple Therapy

No randomized controlled trials have evaluated the efficacy and safety of the combination of warfarin and dual-antiplatelet therapy compared with either therapy alone. There is no reason to expect loss of efficacy when a VKA and dual-antiplatelet therapy are used in combination. It is likely, however, that combination therapy increases the risk of major bleeding, which in patients with an acute coronary syndrome is associated with a 5-fold increased risk of death within 30 days.10

Safety of Triple Therapy

Observational studies of patients receiving triple therapy have reported 30-day major bleeding rates of 0% to 15%, although the upper limit of this range is from a small study and is probably an outlier. Our meta-analysis of 10 studies involving 1349 patients receiving triple therapy revealed a weighted mean incidence of major bleeding at 30 days of 2.2% (95% confidence interval 0.7% to 3.7%; Table).11-20 Most patients in these studies were receiving warfarin for AF and dual-antiplatelet therapy for a coronary artery stent. Although the studies contributing to these estimates were small, involved heterogeneous patient populations, employed different cointerventions, and used various definitions of major bleeding, they provide the best available estimates of bleeding risk associated with triple therapy. Patients and healthcare providers are likely to accept a 2.2% rate of major bleeding at 30 days in patients with a bare-metal stent as an acceptable tradeoff when weighed against the possible consequences of warfarin withdrawal (an increase in the risk of stroke)9 or dual-antiplatelet withdrawal (an increase in the risk of stent thrombosis).9 By contrast, the 1-year bleeding rate is 12%, which highlights the importance of minimizing the exposure to triple therapy.21

Table. Results of a Meta-Analysis of Observational Studies Reporting 30-Day Bleeding Rates in Patients Receiving “Triple Therapy”

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients on TT, n</th>
<th>Mean Age, y</th>
<th>Dual-Antiplatelet Therapy</th>
<th>Warfarin</th>
<th>Bleeding Events at 30 Days, n</th>
<th>Bleeding Rate at 30 Days, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orford et al11</td>
<td>65</td>
<td>N/A</td>
<td>65</td>
<td>26</td>
<td>25</td>
<td>2</td>
</tr>
<tr>
<td>Konstantino et al12</td>
<td>76</td>
<td>64.1</td>
<td>76</td>
<td>76</td>
<td>N/A</td>
<td>2</td>
</tr>
<tr>
<td>Porter et al13</td>
<td>180</td>
<td>65</td>
<td>180</td>
<td>150</td>
<td>67</td>
<td>2</td>
</tr>
<tr>
<td>Lip et al14</td>
<td>6</td>
<td>71.3</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Khurram et al15</td>
<td>107</td>
<td>69</td>
<td>107</td>
<td>n/a</td>
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<td>0</td>
</tr>
<tr>
<td>Rubboli et al16</td>
<td>20</td>
<td>68.9</td>
<td>20</td>
<td>N/A</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Nguyen et al17</td>
<td>580</td>
<td>64</td>
<td>580</td>
<td>580</td>
<td>267</td>
<td>34</td>
</tr>
<tr>
<td>Nguyen et al18</td>
<td>86</td>
<td>N/A</td>
<td>N/A</td>
<td>86</td>
<td>N/A</td>
<td>1</td>
</tr>
<tr>
<td>Rogacka et al19</td>
<td>127</td>
<td>69.9</td>
<td>127</td>
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<td>75</td>
<td>4</td>
</tr>
<tr>
<td>Rossini et al20</td>
<td>102</td>
<td>67.9</td>
<td>102</td>
<td>102</td>
<td>68</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>1349</td>
<td></td>
<td>1263</td>
<td>1153</td>
<td>602</td>
<td>49</td>
</tr>
</tbody>
</table>

Pooled rate 2.2 (0.7–3.7)

TT indicates triple therapy; ACS, acute coronary syndrome.

Treatment Decisions

The Figure presents an algorithm to help physicians select the optimal antithrombotic therapy for patients with AF and a recent coronary artery stent. Because dual-antiplatelet therapy is indicated for all stent patients, the challenge is to identify patients who should also receive warfarin therapy. Dual-antiplatelet therapy alone is likely to be adequate for AF patients undergoing stent insertion who are at low risk of stroke (CHADS2 risk score 0 to 1) and in those at high risk of stroke who are deemed to be at unacceptably high risk of bleeding with triple therapy. Major risk factors for bleeding include advanced age (eg, >75 years), severe renal dysfunction (eg, creatinine clearance <30 mL/min), recent gastrointestinal bleeding (eg, within 6 months), prior stroke, and uncontrolled hypertension (eg, systolic blood pressure >160 mm Hg, diastolic blood pressure >110 mm Hg).22 Patients at high risk of stroke (CHADS2 risk score >1) who are not at high risk of bleeding should be considered for warfarin in addition to dual-antiplatelet therapy. Exposure to triple therapy should be limited by using a bare-metal stent in preference to a drug-eluting stent where possible, thereby restricting the
duration of dual-antiplatelet therapy to 1 month. We believe that for patients who receive a drug-eluting stent and who require triple therapy, the duration of treatment should be limited to 3 months for those with a sirolimus stent and 6 months for those with a paclitaxel stent.

Strategies that may further reduce the risk of bleeding in patients who receive triple therapy include the following:

1. Using the lowest proven effective dose of aspirin: Aspirin should be used at the lowest proven effective dose to reduce the risk of gastrointestinal bleeding. The Anti-thrombotic Trialists' Collaboration analyses showed that aspirin doses of 75 to 100 mg/d were no less effective than higher doses in secondary prevention of major cardiovascular events.22 The CURRENT OASIS-7 (Clopidogrel optimal loading dose Usage to Reduce Recurrent EventS/Optimal Antiplatelet Strategy for InterventionS) investigators showed in invasively

managed patients with acute coronary syndrome that aspirin 75 to 100 mg/d was similarly effective to 300 to 325 mg/d, with no difference in bleeding.24

2. Adding acid-suppressive therapy to prevent gastrointestinal bleeding: The 2008 consensus statement by the American College of Cardiology Foundation/American College of Gastroenterology/American Heart Association recommended a proton pump inhibitor as prophylaxis against gastrointestinal bleeding in patients receiving dual-antiplatelet therapy or in those requiring the combination of antiplatelet and anticoagulant therapy.25 The Food and Drug Administration has issued a warning about the potential for a negative interaction between clopidogrel and proton pump inhibitors based on observational data,26,27 but recent evidence from randomized controlled trials questions whether this interaction is relevant for patients.28,29

3. Ensuring optimal control of international normalized ratio (INR):

The risk of bleeding increases sharply when the INR is above the target therapeutic range. The American College of Cardiology/American Heart Association/Society for Cardiovascular Angiography and Interventions guidelines recommend targeting an INR of 2 to 2.5 for patients receiving triple therapy,30 but the effectiveness and safety of this approach compared with the conventional INR range of 2 to 3 are unproven. Evidence-based methods to optimize anticoagulant control include specialist anticoagulation clinics, self-monitoring with a point-of-care device, and computerized dosing algorithms.30

Case Resolution

Because of the patient’s very high risk of recurrent stroke, he was treated with aspirin 81 mg once daily, clopidogrel 75 mg once daily, and warfarin, targeting an INR of 2.0 to 2.5 for 4 weeks, at which time clopidogrel was discontinued. The same patient receiving a drug-eluting stent instead of a bare-metal stent would continue with triple therapy for 3 or 6 months, at which time clopidogrel would be discontinued. Warfarin was managed by a specialist anticoagulation clinic, and the patient received acid-suppressive therapy to reduce his risk of gastrointestinal bleeding.

Disclosures

Dr Crowther is co-principal investigator on a grant currently before the Canadian Institutes of Health Research examining whether aspirin withdrawal in patients with coronary artery disease and AF results in less bleeding. Dr Crowther holds a Career Investigator Award from the Heart and Stroke Foundation of Canada. Dr Mehra is an investigator for the CURRENT OASIS-7 trial, has received honoraria from Sanofi-Aventis and BMS, and has served as a consultant/advisory board member for Sanofi-Aventis and BMS. Dr Eikelboom is a Coinvestigator for the CURRENT OASIS-7 trial, has received honoraria from Sanofi-Aventis and BMS, and has served as a consultant/advisory board member for Sanofi-Aventis and BMS. The remaining authors report no conflicts.

References

1. McNamara RL, Tamariz LJ, Segal JB, Bass EB. Management of atrial fibrillation: review of the evidence for the role of phar-
macologic therapy, electrical cardioversion, and echocardiography. 


2. Hart RG, Pearce LA, Aguilar MI. Meta-anal-

ysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibril-


pidogrel plus aspirin versus oral anticoagu-


ment of patients with atrial fibrillation: a report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Manage-


8. Schulman S, Beyth RJ, Kearon C, Levine MN. Hemorrhagic complications of antico-


9. Antithrombotic Trials’ Collaboration. Col-


10. Mehta SR on behalf of the CURRENT Steering Committee. A randomized com-

parison of a clopidogrel high loading and maintenance dose regimen versus standard dose and high versus low dose aspirin in 25,000 patients with acute coronary syn-
dromes: results of the CURRENT OASIS-7 Trial. Presented at: European Society of Cardiology Congress 2009; August 30, 2009; Barcelona, Spain. Presentation No. 177.


13. Ho PM, Maddox TM, Wang L, Fihn SD, Jesse RL, Peterson ED, Rumsfeld JS. Risk of adverse outcomes associated with con-

comitant use of clopidogrel and proton pump inhibitors following acute coronary syndrome. JAMA. 2009;301:937–944.


15. Bhatt DL. COGENT: a prospective, ran-

domized, placebo-controlled trial of ome-

prazole in patients receiving aspirin and clo-
pidogrel. Presented at: Transcatheter Cardiovascular Therapeutics; September 24, 2009; San Francisco, Calif.

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