Case Presentation: A 76-year-old man was admitted with retrosternal chest pain. The ECG on admission showed inferolateral ST depression, and troponin levels were elevated, confirming the diagnosis of an acute coronary syndrome. The patient had a history of hypertension and aortic valve replacement with a metallic bileaflet valve 7 years before. He was being treated with warfarin and low-dose aspirin and had an international normalized ratio (INR) of 2.5. Coronary angiography revealed a long sub-occlusive lesion of the proximal right coronary artery. At that point, there was a question about the optimal treatment for this patient regarding the type of stent to be selected and the need for future combined antiplatelet and anticoagulation treatment.

Percutaneous Coronary Intervention and Warfarin Treatment

Oral anticoagulation was routinely used for coronary stent thrombosis prevention during the first era of stents. It has since been replaced by the combination of aspirin and a thienopyridine because studies have shown a definite advantage of the antiplatelet combination on coronary events and on reducing the risk of access-site bleeding complications. However, ≈5% of patients undergoing percutaneous coronary intervention (PCI) also present with an indication for oral anticoagulation therapy. In such cases, the type of stent selected; the use of oral anticoagulants, antiplatelets, or their combinations; the target INR; and the duration of treatment are essential considerations in relation to the risk of stent thrombosis/thromboembolic events and bleeding risk. With the introduction and widespread use of drug-eluting stents (DES) in recent years and given the necessity for longer duration of dual antiplatelet therapy, the issue of concurrent warfarin and antiplatelet therapy has become even more important. The existing guidelines do not offer a convincing solution to these issues. For acute coronary syndrome patients with an indication for anticoagulation, triple therapy (warfarin, aspirin, and clopidogrel) for the minimum time possible and a maintenance regimen of warfarin plus aspirin or clopidogrel was recommended for patients with atrial fibrillation, double therapy of warfarin plus aspirin is recommended after stent implantation for patients with bare metal stents (BMS) was recommended with triple therapy for 1 month, followed by warfarin plus aspirin; DES are to be avoided, but when they are used, clopidogrel therapy for 1 year was recommended. However, these recommendations do not specify the optimal treatment according to the various indications for anticoagulation or the duration of treatment, nor do they take into account the estimated thrombosis and bleeding risks.

As a result, there is a significant variation in the regimens followed for patients on anticoagulation who have had a stent implanted, as was demonstrated in a survey among interventional cardiology centers worldwide. Data from an acute coronary syndrome patient registry show that triple therapy is the most commonly used (60% of acute coronary syndromes), followed by double antiplatelet therapy (used in 31%), whereas warfarin plus aspirin or clopidogrel is used in a minority of patients. However, no randomized trial demonstrating the efficacy and safety of triple therapy has yet been conducted.

A small number of retrospective studies have examined the safety of triple therapy and have demonstrated a significant occurrence of major bleeding episodes, ranging from 4.5% to 27.4% of patients. Data...
from the 3 published matched cohort studies show that the relative risk of major bleeding is 4 times higher with triple therapy than with a standard double antiplatelet regimen (Figure 1). On the other hand, it has been recently demonstrated that double antiplatelet therapy is much less efficient than warfarin alone in preventing embolic episodes in atrial fibrillation patients.23 Even fewer data are available on the efficacy of triple therapy, especially in patients with mechanical valves. Two recent studies18,21 that compared the efficacy of double antiplatelet therapy with combinations, including combinations with warfarin, showed contradictory results in the occurrence of major adverse cardiac events.

Assessment of Individual Risk

Clearly, each of the possible treatments has its pros and cons. The first step in the selection of the appropriate therapy is to assess the risk for each individual, and balancing embolic risk and bleeding risk is crucial in making this decision. Recently published data6 have suggested that cardiologists take bleeding risk into account more than embolic risk, which may have resulted in underuse of warfarin. Although the choice is often based on the subjective empirical estimation of the treating physician, validated schemes for estimating risk are available, and their use is encouraged. The CHADS2 score, a well-tested scheme that has the advantage of simplicity, successfully stratifies atrial fibrillation patients according to risk for stroke. The CHADS2 score is calculated from 5 risk factors: congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, and prior stroke or transient ischemic attack. Two points are given for prior stroke; all the other risk factors are assigned 1 point. A CHADS2 score of 0 to 1 identifies patients at low risk, a score of 2 to 3 marks patients at intermediate risk, and a score of 4 to 6 indicates high-risk patients.24,25

Unlike atrial fibrillation, other conditions put patients at a uniformly high risk of embolism. Patients with a mechanical valve prosthesis have an annual risk of thrombotic complications without anticoagulation that ranges from 10% up to 91%, depending on the type, position, and number of prostheses.26 Patients who have experienced an episode of venous thromboembolism are at an annual risk of 6% to 9% for a subsequent episode. The required duration of anticoagulant treatment is 3 months for an episode resulting from transient causes and 6 months for a recurrent or idiopathic episode.27 A substantial number of patients who

<table>
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<tr>
<th>Authors</th>
<th>Year</th>
<th>Type</th>
<th>Patients, n</th>
<th>Mean Age (Range), y</th>
<th>Regimen</th>
<th>Follow-Up, mo</th>
<th>Major Bleeding,* % (95% CI)</th>
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<tr>
<td>Orford et al13</td>
<td>2004</td>
<td>Retr, Obs</td>
<td>66</td>
<td>73 (63–83)</td>
<td>Triple</td>
<td>NA</td>
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<td>Mattichak et al14</td>
<td>2005</td>
<td>Retr, Obs</td>
<td>82</td>
<td>67 (54–80)</td>
<td>Triple</td>
<td>12</td>
<td>21.4 (13.3±30.8)†</td>
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<tr>
<td>Khurram et al15</td>
<td>2006</td>
<td>Retr, MC</td>
<td>214</td>
<td>69 (58–80)</td>
<td>Triple vs Asp+Clp</td>
<td>7</td>
<td>7.3 (3.0–13.1); OR, 5.4 (2.0–14.5)</td>
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<tr>
<td>Porter et al16</td>
<td>2006</td>
<td>Retr, Obs</td>
<td>180</td>
<td>65 (52–75.5)</td>
<td>Triple</td>
<td>1</td>
<td>1.6 (0.0–4.2)</td>
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<tr>
<td>DeEugenio et al17</td>
<td>2007</td>
<td>Retr, MC</td>
<td>194</td>
<td>70 (59–81)</td>
<td>Triple vs Asp+Clp</td>
<td>6</td>
<td>15.1 (8.7–22.9); OR, 5.0 (1.4–17.8)</td>
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<tr>
<td>Rubboli et al19</td>
<td>2007</td>
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<td>49</td>
<td>68.5 (59–78)</td>
<td>Triple</td>
<td>1</td>
<td>18 (4.4–36.9)</td>
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<td>Karjalainen et al18</td>
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<td>239</td>
<td>70 (61–79)</td>
<td>Triple vs Asp+Clp</td>
<td>12</td>
<td>7.4 (3.0–13.2); OR, 3.3 (1.3–8.6)</td>
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<td>Ruiz-Nodar et al21</td>
<td>2008</td>
<td>Retr, Obs</td>
<td>426</td>
<td>71.5 (63–80)</td>
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<td>Rogacka et al22</td>
<td>2008</td>
<td>Retr, Obs</td>
<td>127</td>
<td>70 (61–79)</td>
<td>Triple</td>
<td>21</td>
<td>5.4 (2–10.1)</td>
</tr>
<tr>
<td>Manzano-Fernandez et al20</td>
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<td>104</td>
<td>72 (64–80)</td>
<td>Triple, Warf+Antiplat, Asp+Clp</td>
<td>12</td>
<td>27.4 (19.3–36.2)</td>
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Retr indicates retrospective; Obs, observational; MC, matched cohort; Asp, aspirin; Clp, clopidogrel; OR, odds ratio; Warf, warfarin; and Antiplat, antiplatelet.

*Midpoint-adjusted Wald interval.
†Transfusions.

Figure 1. Major bleeding in matched cohort trials. Warf indicates warfarin; Asp, aspirin; Clop, clopidogrel; OR, odds ratio; Warf, warfarin; and Antiplat, antiplatelet.
Undergo PCI with stent implantation after an acute myocardial infarction develop left ventricular thrombus and are at increased risk of embolism (6% to 12% annually), so anticoagulation therapy is recommended for at least 3 months for these patients.28

The next step in risk assessment is to estimate the bleeding risk of the patient. Major bleeding in patients under anticoagulant treatment is not rare; the yearly incidence of intracranial hemorrhage was reported to be 0.3% in an elderly population.29 Risk stratification schemes developed so that individual bleeding risk can be objectively estimated30–32 include the Outpatient Bleeding Risk Index, which classifies patients into 3 risk categories: 1 point is applied for age >65 years, 1 point for history of stroke, and 1 point for history of gastrointestinal bleeding; an additional point is applied if any one of the following conditions exists: anemia (hematocrit <30%), renal dysfunction (creatinine >15 mg/L), or diabetes.30 A score of 0 is defined as low risk, 1 to 2 as intermediate risk, and 3 to 4 as high risk for bleeding. This index has been prospectively validated and shown to achieve acceptable discrimination among the categories of risk.32,33

Finally, the selection of the appropriate therapy is influenced by the estimated restenosis risk, which determines whether a DES is necessary. The clinical, lesion, and procedural variables that define high risk for restenosis after BMS implantation are well established;41 however, the concomitant treatment with warfarin urges less liberal use of DES for restenosis prevention because of the risk of increased bleeding inherent in anticoagulation treatment.

**Therapeutic Options**

**Triple Therapy**

The combined use of warfarin, aspirin, and clopidogrel is, in theory, the option that ensures the best protection against embolic episodes and stent thrombosis. Only 2 studies have provided data on the efficacy of triple therapy, showing that its stroke rate is comparable to that on warfarin monotherapy; substantially more data are available on major bleeding caused by the triple combination. Using data from the 3 matched cohort studies (Figure 1), one can estimate that, adding warfarin to standard double antiplatelet therapy, the number needed to harm for 1 year inducing a major bleeding episode was 14. An indirect comparison with the protection provided can be done using data from the Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events (ACTIVE W) study,23 accepting similar rates of stroke for triple therapy and warfarin monotherapy. In the ACTIVE W trial, the number needed to treat to prevent a stroke with warfarin compared with dual antiplatelet therapy was 100. This comparison strongly discourages the extensive use of triple therapy and urges careful selection of patients, but it probably also urges limiting the duration of this treatment.

**Warfarin Plus Aspirin**

The combination of warfarin plus aspirin has been studied much more extensively, although the studies were done before the introduction of latest generation of stents, including DES. A meta-analysis of these studies demonstrated the superiority of double antiplatelet therapy over warfarin plus aspirin in patients with an end point of death, myocardial infarction, or need for revascularization, whereas there was no significant difference in the occurrence of stent thrombosis and major bleeding.35 However, an adjusted indirect meta-analysis based on a much larger number of patients and more recent studies56 showed that the combination of warfarin plus aspirin with a target INR of 2 to 3 was as efficient as aspirin plus clopidogrel in preventing major adverse events in patients recovering from an acute coronary syndrome. The combination of aspirin and warfarin was associated with a lower risk of stroke but increased risk of major bleeding. The number needed to harm to cause a major bleeding episode is 77 compared with 14 with triple therapy. However, the 2 recent trials that provided data on the efficacy of this combination specifically in PCI patients showed a high incidence of stent thrombosis (15.2%) and unscheduled PCI (17.2%), respectively, mainly during the first month of treatment. However, the studies included a small number of patients.18,37

**Warfarin Plus Clopidogrel**

Limited data are available on the safety and efficacy of this combination. In the 2 studies that have addressed the combination,18,37 it presented common major bleeding complications (11.1%) but good efficacy against stroke (0% to 4.4%) and stent thrombosis (0%). However, because these data were derived from a small number of patients, further studies are needed to clarify the issue and support the use of this combination.

**Aspirin Plus Clopidogrel**

The efficacy of the antiplatelet combination against stent thrombosis is well established, especially in the case of DES. In addition, experts suggest warfarin treatment when the risk of stroke is >2%; for lower-risk patients, the benefits from stroke prevention are counterbalanced by the increased bleeding risk, so it is logical to suggest this combination only to patients with a CHADS2 score of 0 to 1. In a recently published study,38 patients with atrial fibrillation and a CHADS2 score of 1 had a yearly stroke risk of 1.25% while taking aspirin plus clopidogrel, which can be considered acceptable, considering the high bleeding risk of other options.

Incorporating the existing data, we provide an algorithm for appropriate treatment selection in various situations in Figure 2.

**Other Considerations**

**Acute Coronary Syndromes**

According to current guidelines, aspirin treatment is recommended definitively for acute coronary syndrome...
patients whether or not they underwent PCI. Clopidogrel is recommended for at least 12 months, especially in the case of coronary stenting. However, in the case of coronary stenting with BMS, the gain from prolonged clopidogrel treatment in patients at intermediate or high risk for bleeding can be assumed to be neutralized by the increased bleeding complications; therefore, we suggest the same strategy as for elective PCI for these patients.

**Access-Site Selection**

It is generally accepted that coronary angiography and PCI can be safely performed by femoral access after discontinuing warfarin and achieving an INR of <1.5,14 Manual-pressure hemostasis and artery closure devices have been used during diagnostic angiography with a low incidence of bleeding complications in fully anticoagulated patients.40,41 However, the usual strategy is to withhold warfarin before transfemoral PCI and to restart after the procedure using intravenous heparin or low-molecular-weight heparin as a bridge until adequate anticoagulation with warfarin is reestablished in patients at high risk for embolism. Many of the bleeding complications are reported to happen during this crossover period from heparin to oral anticoagulation.16 The radial approach has also been used successfully for coronary angiography with no incidence of major bleeding complications in fully anticoagulated patients42,43 and has consistently achieved fewer bleeding complications during PCI compared with the femoral approach.44,45 Compared with the radial approach, femoral access has been a strong predictor of access-site complications after PCI in patients treated with warfarin.46 The possibility of performing PCI by the radial approach without withholding warfarin, thereby avoiding bleeding or thrombotic complications during the crossover period, makes the radial approach the first choice for these patients, especially during emergency procedures.

**Gastric Protection**

Proton pump inhibitors are used in acute coronary syndrome patients considered at high risk for hemorrhage despite the absence of a randomized trial evaluating their usefulness after PCI. However, on the basis of data from a case-control study48 and the documented effectiveness of esomeprazole in reducing bleeding caused by antiplatelet medications,49 proton pump inhibition can be recommended for patients at medium or high risk for bleeding. Omeprazole has been shown to potentiate the anticoagulant action of warfarin50 and to decrease the inhibitory effect of clopidogrel on platelets51; therefore, its use has to be undertaken with caution in this category of patients.52

**Optimal Level of Anticoagulation**

Dual treatment with warfarin and aspirin has been shown to be favorable compared with aspirin monotherapy only in patients under tight INR control and an aim of 2 to 3.53 In the
studies that have provided relevant data, most major bleeding events occurred at INR levels <3.13,17,20 For the duration of concurrent antiplatelet administration, an INR target of 2 to 2.5 under close observation seems to be the best choice. When warfarin therapy is required for a short period of time (eg, venous thromboembolism, left ventricular thrombus), PCI should be postponed, if possible, until completion of warfarin therapy.

Prosthetic Valves
Current guidelines recommend vitamin K antagonists plus low-dose aspirin for patients with mechanical valves and coronary disease. However, long-term triple therapy could increase bleeding complications to unacceptable levels, especially when a high INR target (≥3) is needed because of valve or patient characteristics. Although there are no data available that address this specific subgroup of patients, it seems appropriate to shorten the duration of triple therapy as much as possible and to restrict the use of DES only to patients at low calculated risk for bleeding and with an INR of no more than 2.5.

How Should We Manage Our Example Patient?
Having taken into account the patient’s age and the necessity of anticoagulant treatment, we performed PCI with a BMS. Triple therapy and a proton pump inhibitor were prescribed for 1 month, followed by warfarin with an INR target of 2.5 and aspirin 75 mg indefinitely.

Conclusions
Available data show a remarkably increased rate of major bleeding complications during prolonged treatment with warfarin, aspirin, and thienopyridine. This strongly suggests limiting the time of its administration as much as possible, especially in patients with a high profile for bleeding risk. This might be accomplished in the future by using stents that recruit endothelial progenitor cells and accelerate endothelialization.

A combination of warfarin and 1 antiplatelet agent seems to be a better choice for long-term treatment after stent implantation, balancing the risks of thromboembolic events and stent thrombosis with the risk of major bleeding. Randomized trials in progress are expected to further clarify this issue.

Disclosures
None.

References


43. Lo TS, Buch AN, Hall IR, Hildick-Smith DJ, Nolan J. Percutaneous left and right heart catheterization in fully anticoagulated patients utilizing the radial artery and forearm vein: a two-center experience. J Interv Cardiol. 2006;19:258–263.


