A 64-year-old man has permanent atrial fibrillation and chronic hypertension. He has been treated with atenolol 50 mg daily, lisinopril 10 mg daily, and warfarin for the last 4 years. Otherwise, he is in good shape and employed full-time as a technical director of a large shipbuilding company. At a routine visit about 1 year ago, he complained of chest pain and dyspnea on exertion. An exercise myocardial scintigraphy showed a reversible defect in the anteroseptal region with a normal left ventricular ejection fraction. Simvastatin 40 mg daily was added to his medication, and the dose of atenolol was increased to 100 mg daily. His symptoms persisted and increased over the last several weeks. Coronary angiography showed single-vessel disease of the proximal left anterior descending coronary artery. The heart team decided that the best option would be percutaneous coronary intervention with a drug-eluting stent. During this procedure, the international normalized ratio was tapered to 2.0. The procedure was successful, and he was put on additional aspirin and clopidogrel.

The patient had an uneventful recovery and was free of symptoms. He was seen 3 months after the procedure by his attending cardiologist, who stopped aspirin. One year after the procedure, the patient came for his follow-up visit, and his clopidogrel was discontinued. He remains on atenolol, lisinopril, simvastatin, and warfarin and is doing well.

The Issue of Combined Anticoagulant and Antiplatelet Therapy After Percutaneous Coronary Intervention in Atrial Fibrillation

Intuitively, cardiologists prefer longer dual antiplatelet therapy rather than single antiplatelet medication (aspirin alone) in patients with drug-eluting stents compared with bare metal stents. Consequently, many stented patients are on dual antiplatelet therapy, mainly aspirin and clopidogrel. The only important side effect of dual antiplatelet therapy is increased bleeding compared with aspirin alone. This has been found in the large clopidogrel trials in acute coronary syndromes and in atrial fibrillation. Dual antiplatelet therapy has been shown to be as hazardous as oral anticoagulation with warfarin. Special attention has been given to the risks of dual antiplatelet therapy in patients awaiting coronary artery bypass surgery. Taking clopidogrel with aspirin has been associated with significantly increased blood loss during coronary surgery compared with aspirin alone. However, this excess bleeding was not associated with an increased risk of reoperation or mortality. Yet, it is generally advised that patients discontinue clopidogrel 5 days before coronary surgery. Little is known, however, about the optimal strategy in patients awaiting coronary artery bypass surgery.
on dual antiplatelet therapy undergoing other forms of surgery.

However, the most vexing problem in this field is the use of dual antiplatelet therapy in patients on oral anticoagulation for long-term stroke prevention in atrial fibrillation. When dual antiplatelet therapy was combined with warfarin, bleeding increased by 50% in the Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) trial and 100% to 400% in a large Danish registry.

Recommendations for Combined Anticoagulant and Antiplatelet Therapy After Percutaneous Coronary Intervention in Atrial Fibrillation

The European Society of Cardiology published a position paper on the topic of triple therapy that shows great similarity to North American recommendations: diminished intensity of anticoagulation (international normalized ratio between 2.0 and 2.5), use of low-dose aspirin, and avoidance of the use of drug-eluting stents in patients with high bleeding risk.

The strength of the European approach is that a clear and clinically easy differentiation is made between elective stent implantation and procedures in the setting of acute coronary syndromes with and without ST-segment elevation. In acute coronary syndromes, the thrombus load and thus the thrombotic risk are larger than in stable coronary disease. This is probably true for both the risk of stent thrombosis and the risk of stroke. These differences argue for a more potent approach in the setting of acute coronary syndromes but not necessarily over the long term.

In Europe, a short course of dual antiplatelet therapy (1 month) in elective stenting with a bare metal stent is advised for patients on oral anticoagulants, whereas American recommendations suggest 1 month of dual antiplatelet therapy followed by single antiplatelet therapy (aspirin or clopidogrel) for 12 months (Figure 1).

In a high-thrombotic-risk situation, American experts advise dual antiplatelet therapy for a full year after drug-eluting stent implantation for patients on oral anticoagulation, whereas the Europeans advise dual antiplatelet therapy for 3 months for the modern limus-eluting stents and 6 months for the paclitaxel-eluting stents.

Randomized Clinical Trials for Combined Anticoagulant and Antiplatelet Therapy After Percutaneous Coronary Intervention in Atrial Fibrillation

The What is the Optimal Antiplatelet and Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary Stenting (WOEST) trial randomized 573 patients on oral anticoagulants undergoing stenting to either clopidogrel alone (dual therapy) or clopidogrel plus low-dose aspirin (triple therapy). At 1 year, the primary outcome (Thrombolysis in Myocardial Infarction major, minor, and minimal bleeding) occurred in 19.5% in the dual-therapy group and in 44.9% in the triple-therapy group (hazard ratio, 0.36; 95% confidence interval, 0.26–0.50; P < 0.001; number needed to treat, 4). Myocardial infarction (3.2% versus 4.6%), stroke (1.1% versus 2.8%), target vessel revascularization (7.2% versus 6.7%), and stent thrombosis (1.4% versus 3.2%) did not differ significantly between the groups, but all-cause mortality at 1 year was lower in the dual-therapy group than...
in the triple-therapy group (2.5% versus 6.3%; P=0.027). The combination of the ischemic end points occurred in 11.1% in the double-therapy group and 17.6% in the triple-therapy group (hazard ratio, 0.56; 95% confidence interval, 0.35–0.91; Figure 2). Thus, triple therapy after stenting in warfarin-treated patients doubled the bleeding rate in this randomized trial compared with dual therapy with aspirin omitted (number needed to treat, 4).

Interestingly, thrombotic risk, including stent thrombosis, was not increased by omitting aspirin, and all-cause mortality was reduced by more than half. Of course, this trial was too small to exclude the risk of omitting aspirin in the high-risk population of patients with stent thrombosis or myocardial infarction.

Currently, 2 randomized trials are evaluating the risks and benefits of triple antithrombotic therapy (aspirin, clopidogrel and warfarin) compared with “safer” antithrombotic therapy in anticoagulated patients after coronary stent implantation: the Triple Therapy in Patients on Oral Anticoagulation After Drug Eluting Stent Implantation (ISAR-TRIPLE; NCT00776633) in Germany13 and the Anticoagulation in Stent Intervention trial (MUSICA-2; NCT01141153) in Spain. The outcomes of these trials will guide the management of this difficult group of patients.

**Future Perspectives**

The novel antiplatelet drugs prasugrel and ticagrelor are more effective than clopidogrel in patients with a high thrombotic risk like acute coronary syndromes but in the setting of coronary stenting are not safer.14,15 Novel oral anticoagulants16–18 may also be useful in this setting because they appear safer than warfarin, especially with respect to lower rates of intracranial hemorrhage. The most specific data so far, albeit post hoc and not randomized, come from the RE-LY trial with dabigatran.19 Antiplatelet therapy increased bleeding rate by >50% regardless of the anticoagulant used (warfarin, dabigatran 110 mg twice daily, or dabigatran 150 mg twice daily). The lower bleeding rate of dabigatran 110 mg twice daily compared with warfarin was maintained despite the use of antiplatelet therapy.

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Freek W.A. Verheugt

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