Patients with atrial fibrillation (AF) who have additional risk factors for thromboembolism benefit from chronic anticoagulant therapy (1). When these patients undergo percutaneous coronary intervention (PCI), the need for platelet inhibitor medication poses a particular clinical challenge because the risk of bleeding is significantly increased, especially when “triple therapy” with a combination of warfarin, aspirin, and a thienopyridine is used. Scant data are available to guide management of such patients.

First, consider the imperative of preventing ischemic stroke in patients with AF. Warfarin reduces thromboembolism by about one-half while increasing major bleeding to 1% to 2% per year and doubling the risk of intracranial hemorrhage (2). For the highest-risk AF patients (those with prior stroke, transient ischemic attack, or mechanical heart valves), the benefit of anticoagulation generally outweighs the bleeding risk. On the other hand, low-risk patients can be adequately treated with aspirin alone (1). Analysis of data from 12 randomized trials directly comparing the treatments in 12,721 patients, predominantly for primary prevention, favors anticoagulation with a vitamin K antagonist over antiplatelet therapy (relative risk reduction [RR] about 40%, absolute RR about 1% per year) (2). Anticoagulation was also superior to the combination of aspirin plus clopidogrel in a large trial (6,706 patients; RR reduction 40% [95% confidence interval 18% to 56%]) (3).

The problem stems from differences in the predominant pathophysiological processes involved in myocardial infarction (MI) and ischemic stroke: atherothrombosis versus cardiogenic embolism and the choice of antithrombotic therapy that results. In patients with coronary artery disease, platelet inhibitor therapy is generally prescribed. Although aspirin is the prophylactic antiplatelet drug of choice, it reduces the risk of recurrent stroke, MI, and vascular death by only 13% (4). Clopidogrel was 8% better than aspirin in one large trial and associated with fewer gastrointestinal bleeding complications (5).

After PCI, dual antiplatelet therapy with aspirin plus a thienopyridine is superior to aspirin alone (6,7), warfarin alone, or warfarin plus aspirin (6,8,9). Addition of clopidogrel to aspirin in patients with acute coronary syndromes undergoing PCI significantly reduced rates of myocardial infarction and cardiovascular death (6.0% vs. 8.0%) at an average follow-up of 8 months (7). The trial was underpowered, however, to assess the efficacy of dual antiplatelet therapy compared with aspirin alone for stroke prevention (10). This and other trials support administering the combination of clopidogrel plus aspirin for 4 weeks after elective PCI and for up to 8 months in the acute setting when bare-metal stents (BMS) are used.

The cumulative incidence of target lesion revascularization is lower with drug-eluting stents (DES) (1.9%/year) than with BMS (5%/year), with the majority of events occurring in the first year with either type of device (11). An apparently greater incidence of late stent thrombosis in patients treated with DES, is attributed to delayed re-endothelialization and higher complexity of coronary lesions (12,13). Stent thrombosis with DES can occur beyond the first year and has been associated with interruption of clopidogrel (14).

The inherent risk of prolonged antiplatelet therapy is bleeding (10), which is compounded by adding an anticoagulant. In a secondary analysis of a randomized trial database, addition of aspirin (up to 100 mg daily) in patients with AF who were on warfarin (international normalized ratio 2.0 to 3.0) increased major bleeding (3.9%/year) compared with warfarin alone (2.3%/year, p = 0.01) with-
out reducing stroke and systemic embolism or MI (15). “Triple therapy” has been associated with major bleeding rates as high as 7%/year (16).

In the series of patients with AF undergoing PCI described by Ruiz-Nodar et al. (17), omission of anticoagulation at discharge was associated with increased mortality and major adverse cardiovascular events at a median follow-up interval of 595 days, the longest observation period yet reported. The reduction in adverse events with regimens that included an anticoagulant was mainly attributable to lower rates of mortality and ischemic stroke. Patients with renal failure or acute ST-segment elevation MI were more likely to receive dual antiplatelet therapy without anticoagulation, and this may have contributed to the difference in mortality. There was no significant difference in rates of stent thrombosis between the groups.

The data were derived from retrospective analysis and entailed the considerable variability in the type and duration of antithrombotic therapy that typically characterizes practice in the absence of clear and consistent evidence-based guidelines. These limitations preclude reasonable recommendations regarding the safety and efficacy of triple therapy. Even so, the study highlights the importance of maintaining anticoagulation in patients with AF undergoing PCI. In the absence of randomized trials, physicians must individualize antithrombotic therapy, taking into account the risks of hemorrhage, thromboembolism, and stent thrombosis. Patients with AF who have more than 1 moderate risk factor for thromboembolism (clinical heart failure or impaired left ventricular systolic function [ejection fraction less than or equal to 35%], history of hypertension, age >75 years, diabetes mellitus, prior stroke or transient ischemic attack score = 2 or more) (18) should resume anticoagulation as soon as feasible after PCI. For those at low risk of serious bleeding, treatment with triple therapy may be the option. Perhaps more to the point, BMS may be preferable to DES in patients with AF who have risk factors for thromboembolism requiring chronic anticoagulation to reduce the need for prolonged combination therapy.

A pressing question is whether beyond the first few weeks after stent deployment a maintenance regimen consisting of warfarin plus clopidogrel alone would preserve efficacy while reducing the risk of gastrointestinal bleeding (19). The answer will require additional studies not only in patients with AF but also in the broader population of patients with coronary artery disease who have an ongoing need for anticoagulation.

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