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EDITORIAL COMMENT

Preventing Myocardial Infarction in Patients With Atrial Fibrillation

Another Piece of the Puzzle*

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A conventional tenet of antithrombotic therapy for cardiovascular disease is the use of anticoagulant drugs to prevent formation of fibrin due to activation of the coagulation system in states of hemodynamic stasis, such as occurs in patients with atrial fibrillation (AF). Another is to use antiplatelet drugs to prevent atherothrombotic events, such as myocardial infarction (MI) due to plaque rupture in patients with coronary artery disease. In each situation, the intensity of therapy should be modified in proportion to the risk of thrombotic events. In general, risk is lowest for primary prevention, highest in the early period after an event, and intermediate for long-term secondary prevention during the stable phase of established disease.

The use of aspirin for primary prevention of MI and stroke in the general population has been controversial (1), with its role for prevention of coronary events in patients with concomitant AF even more uncertain. Aspirin is also a standard component of therapy for patients with established ischemic heart disease (2). The efficacy of vitamin K antagonists (VKAs) for secondary prevention after MI has also been known for decades (3,4). The combination of VKA plus aspirin has not resulted in lower rates of mortality, reinfarction, or stroke than has been achieved with aspirin alone and increases the risk of bleeding (5,6).

Relatively few studies have compared the efficacy of VKA versus antiplatelet therapy for primary prevention of atherothrombotic events. TPT (Thrombosis Prevention Trial) found that low-intensity VKA provided greater protection against coronary events than aspirin did in 5,499 high-risk male patients, some of whom had AF (7). For secondary prevention, the WARIS-II (Warfarin-Aspirin Reinfarction Study) study of 3,630 patients found a significant 29% reduction in the composite outcome of death, nonfatal stroke, or nonfatal reinfarction with dual antiplatelet therapy, and 19% with VKA monotherapy compared with aspirin monotherapy (8). The ACTIVE-W (Atrial Fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events) trial found VKA superior to dual antiplatelet therapy with aspirin plus clopidogrel for prevention of reinfarction in 6,706 patients with AF (9).

Anticoagulation is the standard approach to stroke prevention for patients with AF, and its superiority over aspirin is well established (10). Five trials of patients with AF randomized to either VKA or antiplatelet therapy reported rates of MI (11–15). In aggregate, these accumulated 121 MI events, and the frequency did not differ significantly with VKA or antiplatelet therapy.

Whether to add aspirin to an anticoagulant regimen for patients with AF has been a long-standing conundrum. An exploratory analysis of the SPORTIF (Stroke Prevention using an Oral Thrombin Inhibitor in Atrial Fibrillation) trials, which included 7,304 patients, some of whom had concomitant coronary artery disease, found no significant reduction in the rate of MI with aspirin plus VKA compared with VKA monotherapy (16). The antithrombotic approach to primary prevention of MI in patients with AF has not heretofore been specifically addressed.

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In this issue of the *Journal*, Lee et al. (17) report an analysis of 71,959 patients with AF (median 75 years of age) in the Danish National Patient Registry who

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did not have known coronary disease. The dataset, from one of the world's oldest nationwide hospital registries, includes all patients discharged from nonpsychiatric hospitals in Denmark after 1978. The ability to accurately identify diagnoses such as AF and MI has been validated; other diagnoses pertinent to the analysis were identified by International Classification of Diseases codes.

Patients received VKA monotherapy, aspirin monotherapy, or various combinations of both VKA and aspirin, and it is noteworthy that in this nonrandomized study, aspirin-treated patients were generally older and seemingly at higher intrinsic risk of ischemic events than were those managed otherwise. Over an average follow-up of 16 years, the incidence rate of MI was 0.8% per 100 patient-years, and patients treated with VKA monotherapy had a lower incidence of MI than did those taking aspirin monotherapy. Furthermore, the combination of both an anticoagulant and antiplatelet agent not only did not reduce the rate of MI but also was associated with more bleeding requiring hospitalization.

As in many other countries, aspirin is available without prescription in Denmark, so it is not possible to know for certain how many patients classified as taking VKA monotherapy might have taken aspirin concurrently, nor can we be sure about the doses of aspirin actually taken. Furthermore, patients taking clopidogrel or other antiplatelet agents, either as monotherapy or as part of dual antiplatelet regimens, were not included. Several types of VKA drugs (warfarin and phenprocoumon) were used in Denmark during the observation period. This, the quality of anticoagulation control, intrinsic patient risk, and concomitant medical therapy are additional clinical variables that could influence outcomes on an individual patient basis.

These considerations notwithstanding, the report by Lee et al. (17) should prompt clinicians to rethink the approach to antithrombotic therapy for patients with AF, particularly when anticoagulation is indicated in those at more than minimal thromboembolic risk. Although the risk of stroke in patients with AF generally exceeds their risk of MI, the latter is not negligible, even when the diagnosis of coronary disease has not been established. The risk of MI seems lowest when patients are treated with an anticoagulant, highest among those treated with aspirin alone, and intermediate for those treated with both, but combination therapy carries a greater risk of major bleeding than either form of monotherapy does. As for stroke, the risk was greatest among those taking aspirin, either alone or in combination with a VKA.

For patients with AF and known coronary atherosclerosis, the risk of MI is higher and the question of whether to add an antiplatelet agent to an anticoagulant may seem more challenging. Available data suggest, however, that the answer may be the same—anticoagulation alone has been associated with low rates of MI (generally <1%/year) in randomized trials. In the era of target-specific anticoagulants, it is worth noting that no significant differences in rates of MI, which ranged from 0.5%/year to 1.1%/year, were observed in the 5 randomized trials comparing target-specific oral anticoagulants against warfarin for patients with AF, in which the prevalence of prior MI ranged from about 14% to 18% (18). Hence, although these newer anticoagulants are not addressed in the report by Lee et al. (17), there is reason to believe that efficacy rates for MI would be similar, even if rates of major bleeding, particularly intracerebral hemorrhage, might be lower.

Combination therapy is necessary for most patients with AF who suffer an acute coronary syndrome or undergo percutaneous coronary intervention with stenting. In such cases, a period of dual antiplatelet therapy is generally recommended and anticoagulation is sometimes temporarily interrupted, but these strategies have been cast into doubt in 2 respects. First, the need for aspirin in addition to a thienopyridine or P_2Y_{12} inhibitor is uncertain, as one of the more potent agents alone may suffice, the combination increases the risk of bleeding compared with antiplatelet monotherapy, and it is not clear whether aspirin adds or detracts from therapeutic efficacy. The duration of therapy may vary with the number, location, and types of stents deployed, but seldom needs to exceed 12 months (19). Trials of target-specific oral anticoagulants in combination with antiplatelet drugs in this situation suggest that safety can be improved compared with warfarin, but relative efficacy is difficult to establish with certainty (20).

The work of Lee et al. (17) adds important information that can be applied clinically in managing the risk of both stroke and MI in patients with AF, and should reduce the tendency to add aspirin to an anticoagulant for those without known coronary disease and perhaps even for those with stable ischemic heart disease. Important questions remain about optimal antithrombotic strategies for patients in more acute situations, such as those who have recently sustained MI or undergone revascularization, and ongoing trials are likely to shed more light on these as well.

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