EDITORIALS

Atrial Fibrillation and Stable Coronary Artery Disease

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Patients with atrial fibrillation are at high risk for stroke, and international guidelines recommend oral anticoagulant therapy. In patients with stable vascular disease without atrial fibrillation, antiplatelet therapy is recommended. However, atrial fibrillation commonly coexists with vascular diseases, such as coronary artery disease. When patients with both conditions present with an acute coronary syndrome or need to undergo percutaneous coronary intervention for implantation of a stent, management with oral anticoagulant therapy plus antiplatelet therapy is clearly supported by evidence from randomized trials. However, the evidence base is less clear for patients with atrial fibrillation and stable vascular disease. The clinician has to balance the need to reduce the long-term risk of thrombotic events against the potential for serious bleeding, which is accentuated when oral anticoagulant therapy is combined with antiplatelet agents.

In patients with stable vascular disease without atrial fibrillation, the COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) trial showed that treatment with rivaroxaban at a dose of 2.5 mg twice daily plus aspirin led to better cardiovascular outcomes but a higher incidence of major bleeding events than treatment with aspirin alone.[1] However, the rivaroxaban regimen used in the trial was different from the stroke-prevention regimen used for patients with atrial fibrillation.

In patients with both atrial fibrillation and stable coronary artery disease, the AFIRE (Atrial Fibrillation and Ischemic Events with Rivaroxaban in Patients with Stable Coronary Artery Disease) trial compared rivaroxaban monotherapy with combination therapy (rivaroxaban plus a single antiplatelet agent) and showed that monotherapy was noninferior with regard to efficacy and superior with regard to safety.[2] This trial was stopped early because of higher mortality in the combination-therapy group, and the rivaroxaban dose used in the trial was not the dose used worldwide for thromboprophylaxis in patients with atrial fibrillation.

Cho et al.[3] now report in the *Journal* the results of the EPIC-CAD (Edoxaban versus Edoxaban with Antiplatelet Agent in Patients with Atrial Fibrillation and Chronic Stable Coronary Artery Disease) trial, which compared edoxaban monotherapy with combination therapy (edoxaban plus a single antiplatelet) in patients with atrial fibrillation and stable coronary artery disease. At 12 months, the cumulative incidence of a primary outcome event — a composite of death from any cause, myocardial infarction, stroke, systemic embolism, unplanned urgent revascularization, or major bleeding or clinically relevant nonmajor bleeding — was lower with monotherapy than with combination therapy (hazard ratio, 0.44; 95% confidence interval [CI], 0.30 to 0.65; P<0.001). This difference was essentially due to a lower incidence of bleeding among the patients who received edoxaban monotherapy (hazard ratio, 0.34; 95% CI, 0.22 to 0.53). The EPIC-CAD trial is an important, well-conducted clinical trial that provides further evidence supporting the use of thromboprophylaxis with oral anticoagulation monotherapy in patients with atrial fibrillation and associated stable vascular disease.

Nevertheless, the results of the trial need to be put into perspective. Although it is often assumed that stroke related to atrial fibrillation is a cardioembolic event, competing atherosclerotic

causes of stroke may be present, including carotid artery disease and intracranial vessel stenosis, which is common in Asian populations. The EPIC-CAD trial (as well as the AFIRE trial) included patients with coronary artery disease only, and whether the findings are fully translatable to patients with stable disease in other vascular areas (e.g., peripheral, aortic, or carotid regions) is uncertain. Patients with atrial fibrillation and stable noncoronary vascular disease are clearly at high risk for cardiovascular events,[4] and it would seem reasonable to also treat them with oral anticoagulation monotherapy, in line with evidence-based treatment recommendations for patients with coronary artery disease. Also, the EPIC-CAD trial (and the AFIRE trial) only included Asian patients, and differences with regard to ethnic group in the risk thrombotic events and the risk of bleeding are evident when comparing Asian cohorts with non-Asian cohorts.[5,6] Therefore, further studies involving non-Asian cohorts may be needed.

The results of the EPIC-CAD trial were largely consistent across the various subgroups assessed by the authors, but monotherapy seemed to have had a greater beneficial effect in men than in women, which was also shown in the AFIRE trial. Differences with respect to sex in the incidence of stroke and the incidence of bleeding among patients with atrial fibrillation have been the subject of much focus recently, and older data show that the risk of stroke is higher among female patients than among male patients.[7] However, more recent data suggest that the difference in the risk of stroke between male patients and female patients is now nonsignificant, which has implications for risk stratification for stroke.[8]

The incidence of ischemic events was similar in the treatment groups in the EPIC-CAD trial (and the AFIRE trial), although the incidence of death from any cause was higher in the combination-therapy group than in the monotherapy group in the AFIRE trial. Nevertheless, both trials were probably underpowered to detect differences in the risk of ischemic events and the risk of death between the treatment groups. The most striking result in each trial was the higher risk of bleeding in the combination-therapy group. Nonetheless, we should not forget that bleeding risk is influenced by the interaction between modifiable and nonmodifiable risk factors for bleeding. Proactive management of the bleeding risk with the use of the HAS-BLED score in order to mitigate modifiable risk factors and identify high-risk patients was associated with a lower incidence of major bleeding at 1 year than usual care, with a relative increase in oral anticoagulation use.[9] In any case, bleeding risk (and stroke risk) in atrial fibrillation is associated with coexisting conditions and can change in a dynamic manner with aging and incident coexisting conditions.

Finally, the EPIC-CAD trial showed that combination therapy with an oral anticoagulant plus an antiplatelet agent in patients with stable coronary artery disease was associated with a greater risk of bleeding than edoxaban monotherapy, with no reduction in the risk of ischemic events. Any bleeding events in patients with atrial fibrillation are always a red flag for adverse clinical outcomes.[10] When bleeding occurs in clinical practice, oral anticoagulant therapy is often discontinued, but the prognosis in this situation is much worse than if treatment with the oral anticoagulant is continued.[10] The EPIC-CAD trial provides additional reassurance for prescribing oral anticoagulant monotherapy for patients with atrial fibrillation and stable vascular disease.

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Prevention of Cardiovascular Disease — Don't Stop Thinking about Tomorrow

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Taking a long-term view of cardiovascular disease prevention is an attractive strategy since atherosclerosis begins early in life and progresses over decades. Lowering low-density lipoprotein (LDL) cholesterol levels and improving lifestyle habits are mainstay strategies for reducing the risk of cardiovascular disease.[1] Moreover, emerging therapeutic targets include vascular inflammation as reflected by elevated levels of high-sensitivity C-reactive protein (CRP) and lipoprotein(a).

Ridker et al. now report in the *Journal* the results of an examination of the long-term predictive value of a single baseline measurement of high-sensitivity CRP, LDL cholesterol, and lipoprotein(a) levels in nearly 28,000 healthy, female, U.S. health professionals enrolled in the Women's Health Study.[2] The mean age of the participants was 54.7 years, 94.0% were White, and the median follow-up was 27.4 years. A total of 3662 first major adverse cardiovascular events occurred, and quintiles of increasing baseline levels of high-sensitivity CRP, lipoprotein(a), and LDL cholesterol each predicted the 30-year risk of cardiovascular disease. When the top quintile was compared with the bottom quintile for each biomarker, the adjusted hazard ratios for a first major adverse cardiovascular event were 1.70 (95% confidence interval [CI], 1.52 to 1.90) for high-sensitivity CRP, 1.36 (95% CI, 1.23 to 1.52) for LDL cholesterol, and 1.33 (95% CI, 1.21 to 1.47) for lipoprotein(a). These hazard ratios were adjusted for age, initial randomization of patients to receive aspirin or vitamin E, smoking status, the presence of diabetes, and blood pressure. In a model that included all three biomarkers, each one had an independent association with risk; moreover, the risk was additive with different combinations of elevated biomarker levels, and the risk was highest when the levels of all three were elevated.

This cohort of female health professionals enrolled in the Women's Health Study had a high degree of access to medical care. In addition, the mean body-mass index (the weight in kilograms divided by the square of the height in meters) was 25.9, and only 2.5% of the participants had diabetes, both of which reflected better cardiometabolic health than the current general U.S. population. More than half the women eventually began receiving statin therapy, which would have reduced the risk of cardiovascular disease related to LDL cholesterol. In an analysis in which follow-up data were censored at the time of statin initiation, the risk associated with high-sensitivity CRP was similar to the risk associated with LDL cholesterol, with hazard ratios of 1.65 and 1.62, respectively, for the top quintile as compared with the bottom quintile.

The fact that the associations of LDL cholesterol, high-sensitivity CRP, and lipoprotein(a) with the risk of cardiovascular disease were seen over 30 years is powerful evidence of the importance of these measures for the prediction of risk. Levels of lipoprotein(a) are at least 90% genetically determined, and a single measurement can reflect long-term cumulative exposure. LDL cholesterol and high-sensitivity CRP are more dynamic markers for which multiple measurements would probably have been even more informative.

Ridker et al. provide a clear description of the concept of long-term risk of cardiovascular disease. This concept of 30-year risk of cardiovascular disease is emphasized in the American Heart Association's recent definition of cardiovascular–kidney–metabolic syndrome, which re-