EDITORIAL

Antithrombotic Therapy in Atrial Fibrillation and Coronary Artery Disease

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The Food and Drug Administration approved the first direct oral anticoagulant nearly a decade ago. Since then, antithrombotic therapy has evolved swiftly, with research systematically addressing the use of these agents for the treatment of common medical conditions, such as atrial fibrillation. Of particular concern in recent years has been the question of how to manage atrial fibrillation and coronary artery disease when they occur together in the same patient.

Yasuda and colleagues[1] now report in the *Journal* the results of the AFIRE (Atrial Fibrillation and Ischemic Events with Rivaroxaban in Patients with Stable Coronary Artery Disease) trial. This multicenter, open-label trial involved 2236 patients with atrial fibrillation who had undergone percutaneous coronary intervention (PCI) (in 70% of the patients) or coronary-artery bypass grafting (CABG) (in 11%) more than 1 year earlier or who had angiographic coronary artery disease not leading to revascularization (i.e., stable coronary artery disease). These patients were randomly assigned to receive either rivaroxaban monotherapy (at the standard approved dose in Japan) or combination therapy with rivaroxaban plus a platelet inhibitor (aspirin or a $P2Y_{12}$ receptor antagonist); approximately 25% of the patients received clopidogrel. The trial was stopped after a median treatment duration of 23 months because of a higher incidence of death from any cause in the combination-therapy group.

The rate of the composite of death, stroke, systemic embolism, myocardial infarction, or unstable angina requiring revascularization (the primary efficacy end point) was 4.14% per patient-year in the monotherapy group and 5.75% per patient-year in the combination-therapy group (hazard ratio, 0.72; 95% confidence interval [CI], 0.55 to 0.95; P<0.001 for noninferiority). Monotherapy was superior to combination therapy for major bleeding (the primary safety end point), according to the criteria of the International Society on Thrombosis and Hemostasis, with rates of 1.62% and 2.76% per patient-year, respectively (hazard ratio, 0.59; 95% CI, 0.39 to 0.89; P=0.01 for superiority). In the final analysis, there were more deaths from noncardiovascular causes (30 vs. 15) and more cardiovascular deaths (43 vs. 26) in the combination-therapy group, a result that the investigators acknowledge was not expected.

The AFIRE trial followed a similarly designed but inconclusive trial called OAC-ALONE (Optimizing Anti-Thrombotic Care in Patients with Atrial Fibrillation and Coronary Stent),[2] which included patients with stable coronary artery disease and atrial fibrillation who received an oral anticoagulant (a vitamin K antagonist or direct oral anticoagulant) alone or in combination with either aspirin or clopidogrel. The primary outcome of death from any cause, myocardial infarction, stroke, or systemic embolism (median follow-up, 2.5 years) occurred in 54 patients (15.7%) in the monotherapy group and in 47 (13.6%) in the combination-therapy group (hazard ratio, 1.16; 95% CI, 0.79 to 1.72; P=0.20 for noninferiority). Major bleeding occurred in 27 patients (7.8%) and 36 patients (10.4%), respectively. The trial was stopped after 696 of the in-

tended 2000 patients were enrolled because of slow enrollment.

The combination of atrial fibrillation with active coronary artery disease (a recent acute coronary syndrome, recent PCI, or both) has been the focus of several randomized clinical trials, and a network meta-analysis involving more than 10,000 patients was recently completed.[3] As compared with a regimen of a vitamin K antagonist plus dual antiplatelet therapy, the odds ratios for TIMI (Thrombolysis in Myocardial Infarction) major bleeding were 0.58 (95% CI, 0.31 to 1.08) for a vitamin K antagonist plus a $P2Y_{12}$ inhibitor, 0.49 (95% CI, 0.30 to 0.82) for the standard approved dose of a direct oral anticoagulant plus a $P2Y_{12}$ inhibitor, and 0.70 (95% CI, 0.38 to 1.23) for a direct oral anticoagulant plus dual antiplatelet therapy. As compared with a vitamin K antagonist plus dual antiplatelet therapy, the odds ratios for a major adverse cardiovascular event were 0.96 (95% CI, 0.60 to 1.46) for a vitamin K antagonist plus a $P2Y_{12}$ inhibitor, 1.02 (95% CI, 0.71 to 1.47) for a direct oral anticoagulant plus a $P2Y_{12}$ inhibitor, and 0.94 (95% CI, 0.60 to 1.45) for a direct oral anticoagulant plus dual antiplatelet therapy. The incidence of intracranial hemorrhage was higher with aspirin-containing regimens than with regimens that did not contain aspirin. On the basis of these data, current guidelines recommend a short period of triple therapy (an oral anticoagulant plus aspirin and a $P2Y_{12}$ inhibitor) followed by dual therapy with an oral anticoagulant plus a $P2Y_{12}$ inhibitor for a period ranging from 1 to 12 months.[4-6]

However, these recommendations apply only to patients who have a combination of atrial fibrillation and active coronary disease. They do not address the question of how to treat patients with atrial fibrillation who have stable coronary disease. Do the collective data from the AFIRE and OAC-ALONE trials provide definitive guidance for clinicians who are treating patients in this population? In my judgment, they do add an element of support for current guidelines[7] and underscore the potential effect of direct oral anticoagulants on the pathobiology of coronary artery disease and cardioembolic events in patients with atrial fibrillation,[4,8,9] but they fall short of securing level 1 and class A evidence. Further investigation will be required.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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1. Yasuda S, Kaikita K, Akao M, et al. Antithrombotic therapy for atrial fibrillation with stable coronary disease. N Engl J Med. DOI: 10.1056/NEJMoa1904143.
2. Matsumura-Nakano Y, Shizuta S, Komasa A, et al. Open-label randomized trial comparing oral anticoagulation with and without single antiplatelet therapy in patients with atrial fibrillation and stable coronary artery disease beyond 1 year after coronary stent implantation. Circulation 2019;139:604-16.
3. Lopes RD, Hong H, Harskamp RE, et al. Safety and efficacy of antithrombotic strategies in patients with atrial fibrillation undergoing percutaneous coronary intervention: a network meta-analysis of randomized controlled trials. JAMA Cardiol 2019 June 19 (Epub ahead of print).
4. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2019;74:104-32.
5. Valgimigli M, Bueno H, Byrne RA, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: the Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2018;39:213-60.
6. Mehta SR, Bainey KR, Cantor WJ, et al. 2018 Canadian Cardiovascular Society/Canadian Association of Interventional Cardiology focused update of the guidelines for the use of antiplatelet therapy. Can J Cardiol 2018;34:214-33.
7. Lip GYH, Collet JP, Haude M, et al. 2018 Joint European consensus document on the management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous cardiovascular interventions: a joint consensus document of the European Heart Rhythm Association (EHRA), European Society of Cardiology Working Group on Thrombosis, European Association of Percutaneous Cardiovascular Interventions (EAPCI), and European Association of Acute Cardiac Care (ACCA) endorsed by the Heart Rhythm Society (HRS), Asia-Pacific Heart Rhythm Society (APHRS), Latin America Heart Rhythm Society (LAHRS), and Cardiac Arrhythmia Society of Southern Africa (CASSA). Europace 2019;21:192-3.
8. Feldmann K, Grandoch M, Kohlmorgen C, et al. Decreased M1 macrophage polarization in dabigatran-treated Ldlr-deficient mice: implications for atherosclerosis and adipose tissue inflammation. Atherosclerosis 2019;287:81-8.
9. Lee J, Nakanishi R, Li D, et al. Randomized trial of rivaroxaban versus warfarin in the evaluation of progression of coronary atherosclerosis. Am Heart J 2018;206:127-30.

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