RESEARCH LETTER

Rivaroxaban Monotherapy in Patients With Atrial Fibrillation and Coronary Stenting at Multiple Vessels or the Left Main Trunk: The AFIRE Trial Subanalysis

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The atrial fibrillation and ischemic events with rivaroxaban in patients with stable coronary artery disease (AFIRE) trial demonstrated that rivaroxaban monotherapy is noninferior to combination therapy with rivaroxaban plus a single antiplatelet agent for cardiovascular events and death, and superior for major bleeding in patients with atrial fibrillation and stable coronary artery disease (CAD). However, the risk for ischemic events may vary depending on the severity of CAD in patients who received percutaneous coronary intervention. Coronary lesions in multiple vessels or the left main trunk (LMT) are considered a more severe type of CAD. It is unclear whether the results of the AFIRE trial are consistent in these patients at high-risk of ischemic events.

The AFIRE trial randomly assigned 2240 patients with atrial fibrillation and stable CAD to receive either monotherapy with rivaroxaban or combination therapy with rivaroxaban plus an antiplatelet agent. This trial was approved by an institutional review committee and the subjects gave informed consent. A total of 1402 patients who underwent coronary stenting before enrollment were chosen for this AFIRE trial subanalysis and were divided into 2 subgroups: patients receiving stenting in 1 vessel (1V, n=1020) and in multiple vessels or LMT (MV/LMT, n=382). The primary efficacy end point was the composite of stroke, systemic embolism, myocardial infarction, unstable angina requiring revascularization or death from any cause. The primary safety end point was International Society on Thrombosis and Hemostasis major bleeding. Cumulative event rates were estimated using the Kaplan–Meier method and log-rank test was performed to assess differences among groups. We compared the outcomes between treatment groups, using Cox proportional hazard analysis. The treatment effect in each subgroup was examined in separate models. The P value for interaction was assessed to examine the heterogeneity in subgroups. Statistical analyses were conducted using JMP 16.0.0. Study data are available from the corresponding author upon reasonable request.

There were no significant differences in major backgrounds between the treatment arms in both 1V and MV/LMT subgroups. Relative risks according to each

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*A complete list of the AFIRE Investigators has been provided as a Supplemental Material file.

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**Figure.** Relative risk of the primary efficacy end point, the primary safety end point, and the components of the efficacy end point according to each subgroup.

The primary efficacy end point was composite of stroke, systemic embolism, myocardial infarction, unstable angina requiring revascularization, or death from any cause. The primary safety end point was major bleeding. Data are presented as incidence rate (total events) per 100 person-years. 1V indicates 1 vessel; Combi, combination therapy; LMT, left main trunk; Mono, rivaroxaban monotherapy; and MV, multiple vessels.
subgroup are shown in the Figure. There were no statistically significant differences in the primary efficacy end point between the treatment arms in both 1V (hazard ratio [HR] 0.75 [95% CI, 0.50–1.11; P=0.15]) and MV/LMT (HR, 0.59 [95% CI, 0.31–1.12; P=0.11]) subgroups and there was no significant interaction (P for interaction 0.55). In contrast, there was a statistically significant difference in the primary safety end point in MV/LMT (HR, 0.16 [95% CI, 0.05–0.53; P<0.01]) subgroup, while not in 1V (HR, 0.88 [95% CI, 0.49–1.57; P=0.66]) subgroup. There was a significant interaction between 1V and MV/LMT subgroups in terms of safety (P for interaction 0.01). This was also the case with other bleeding end points, including any bleeding, nonmajor bleeding, and gastrointestinal bleeding (data not shown). In addition, in patients with coronary stenting in the LMT (n=4; 24 with monotherapy and 22 with combination therapy), neither primary efficacy nor safety end points occurred in the monotherapy group (efficacy/safety end points: monotherapy 0/0, combination therapy 1/3).

The rates of repeat revascularization, stent thrombosis, and death were reported to be higher in patients with complex CAD lesions than simpler lesions. Thus, in more severe types of CAD, more potent anti-thrombotic therapy, including combinations of anti-thrombotic drugs, has been recommended. However, this sub-analysis did not support the advantage of combination therapy, even for patients with a high-risk of ischemic events. Another subanalysis of the AFIRE trial also demonstrated that the advantage of rivaroxaban monotherapy was consistent even in a high-risk subgroup of patients with prior atherothrombotic disease (myocardial infarction, stroke, and/or peripheral artery disease). Patients with complex CAD concomitantly have features that significantly increase their bleeding risk such as multiple comorbidities, renal dysfunction, or previous bleeding. With respect to bleeding, the benefit of rivaroxaban monotherapy was considered to be greater in patients with MV/LMT because such patients were considered to have multiple morbidities and poorer clinical backgrounds. In a subanalysis of the management of high bleeding risk patients post bioresorbable polymer coated stent implantation with an abbreviated versus standard DAPT regimen (MASTER DAPT) trial, abbreviated antiplatelet regimen after percutaneous coronary intervention did not result in the increase in net adverse events in patients with indication for oral anticoagulants, as compared with nonabbreviated regimen. Therefore, rivaroxaban monotherapy may be not only sufficient to prevent thromboembolic events even in patients with a high-risk for ischemic events, but also superior to combination therapy through fewer bleeding events.

Our study has several limitations, in addition to those described in the main article. We did not collect information on the disease severity scale such as SYNTAX score; a patient who had severe and diffuse coronary disease but received stenting only in 1 vessel may have been included in 1V subgroup. Patients with advanced CAD may have been excluded from the trial. Lastly, the number of events was relatively low, limiting statistical power. Among patients with atrial fibrillation after percutaneous coronary intervention, the effects of rivaroxaban monotherapy for the efficacy and safety end points were consistent irrespective of coronary complexity, and the benefit was even greater in patients receiving stenting in MV/LMT than 1V regarding the safety end point.

**ARTICLE INFORMATION**

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Supplemental Material
Appendix S1. AFIRE Study Committees and Investigators

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