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Atrial Fibrillation and Ischemic Events With Rivaroxaban in Patients With Stable Coronary Artery Disease **(AFIRE) Trial**
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Background

ACC/AHA/HRS 2019 update to 2014 Afib Guidelines:
Following coronary revascularization (percutaneous or surgical) in patients with AF & CHA2DS2-VASc ≥ 2, it may be reasonable to use clopidogrel(75 mg QD) + oral anticoagulant (Class IIb)

ESC/EACTS 2017:
Patients with indication for oral anticoagulation (e.g. AF) undergoing PCI may continue Dual Therapy of OAC + Single Antiplatelet for up to 12 months

AUGUSTUS 2019:
Patients with AF & recent ACS or PCI treated with Apixaban + P2Y12 inhibitor without aspirin, resulted in less bleeding and fewer hospitalizations after 6 months.

WOEST (2013):
Compared the use of Clopidogrel +/- ASA in patients on OAC therapy undergoing PCI that showed a reduction in both bleeding & ischemic events by d/c ASA in patients on oral anticoagulation with VKA and undergoing PCI. However, the trial was small and underpowered for this analysis. (N=573)

PIONEER AF-PCI (2016):
Compared 2 regimens of Rivaroxaban and VKA. (15mg QD + P2Y12) vs. (2.5mg BID + ASA + P2Y12 with switch to 15mg QD + ASA when P2Y12 was d/c) vs. (VKA + DAPT). The incidence of bleeding was significantly lower in the Rivaroxaban regimens than with the VKA regimen with no significant increase in risk of ischemic events, stroke, or stent thrombosis

RE-DUAL PCI (2017):
Compared 2 antithrombotic regimens of approved doses of dabigatran 150mg BID or 110mg BID + P2Y12 vs. VKA + DAPT. Rates of bleed significantly lower in dabigatran regimens than in VKA regimens without significantly higher rate of ischemic events. However, this study compared Double vs Triple Therapy

- **(Neither PIONEER nor RE-DUAL designs able to determine if lower bleed risk was due to use of DOAC, reduced dose of the DOAC, or D/C of ASA)**

Van Rein et. al (2019):
Nationwide Danish cohort that assessed rates of major bleed in AF patients in Single, Dual, or Triple therapy. Triple therapy in AF patients had high rates of bleed compared to Dual/Monotherapy.

OAC-ALONE (2019):
Investigated the use of oral anticoagulant monotherapy in AF and stable CAD at more than 1 year post-stent, but enrollment was terminated early and was underpowered and inconclusive for this assessment.

- Current consensus & guidelines recommend combination therapy of oral anticoagulant + P2Y12 up to 1 year post-PCI in AF patients.

Purpose & Objective	● Current guidelines recommend OAC monotherapy with no antiplatelets beyond 1 year post-PCI, based on 2019 Danish cohort study, but this recommendation is not yet supported with evidence from randomized clinical trials, which is a gap in evidence that this study intends to address. ● Investigate whether Rivaroxaban monotherapy is noninferior to combination therapy (Rivaroxaban + antiplatelet) in patients with Nonvalvular Afib (NVAF) & stable CAD more than 1 year post-revascularization OR in Angiography-confirmed CAD not requiring revascularization.

Methods

Study Design	The AFIRE Trial was a multicenter, randomized, phase 4, open-label, parallel-group trial involving 294 Centers in Osaka, Japan

Inclusion Criteria	**Exclusion Criteria**
Patients with: ● Non-valvular atrial fibrillation complicated with stable coronary artery disease who are 20 years or older, with CHADS2 score are ≧1 , and that fulfill one of the following criteria will be eligible. Patients who: ● Underwent PCI, including POBA, at least one year ago ● Have coronary stenosis requiring no percutaneous coronary intervention (50% or more stenosis) as indicated by coronary CT or CAG ● Underwent CABG at least one year ago	Patients for whom: ● Rivaroxaban is contraindicated ● Aspirin, P2Y12 inhibitors are contraindicated ● Underwent PCI, including POBA, in the past one year ● Going to undergo revascularization ● Have a past history of stent thrombosis ● Going to undergo invasive surgery (excluding digestive endoscopy and biopsy) ● Active tumors ● Poorly-controlled hypertension (SBP of 160 mmHg or more) ● Cannot D/C treatment with antiplatelet drugs

Allocation	Randomly assigned patients in a 1:1 ratio to receive either Rivaroxaban Monotherapy (10 mg once-daily; for patients with CrCl [15-49] or 15 mg for patients with CrCl >50. Or Combination therapy of Rivaroxaban + Aspirin or P2Y12 Inhibitor (Clopidogrel or Prasugrel).
Intervention(s)	Rivaroxaban **[Monotherapy]** ● Rivaroxaban will be orally administered after a meal at 15 mg if CrCl ≥50 mL/min or 10 mg if CrCl 15-49 mL/min (regardless of time) Rivaroxaban and Single Antiplatelet (aspirin, clopidogrel or prasugrel) **[Combination]** ● 81-100mg Aspirin will be orally administered once a day at a dose of 81 mg or 100 mg ● Clopidogrel will be orally administered once a day after a meal at a dose of 75 mg. The dose will be reduced to 50mg once a day depending on age, body weight or clinical findings. ● Prasugrel will be orally administered once a day at a dose of 3.75 mg. ○ If the body weight is 50kg or less a reduced dose(2.5 mg once a day) will be considered depending on the age, renal function or other bleeding and thrombotic risk.
Endpoints	Primary Endpoint ● Cardiovascular Events or Death from any cause Primary Safety Endpoint ● Major Bleeding (according to the criteria of the International Society on Thrombosis and Hemostasis) 1. Bleeding accompanied by a reduction in hemoglobin of 2 g/dL or more 2. Bleeding requiring 2 or more units of blood transfusion (packed red blood cells or whole blood)– According to US and European standards, 1 unit is 450 to 500 mL, however, this study complies with the Japanese standard of 200 mL per unit 3. Bleeding in important organs (intracranial, intraarticular, intraocular/retinal, intramuscular with compartment syndrome, intrathecal, intrapericardial, or retroperitoneal bleeding) 4. Bleeding leading to death Secondary Endpoints ● Death from any cause ● Composite of ischemic cardiovascular events or death ○ Death from any cause, MI, Unstable Angina requiring revascularization, Stroke, TIA, Systemic Arterial Embolism, VTE, Revascularization, or Stent Thrombosis
Statistical Analysis	● The trial was powered to assess the noninferiority of rivaroxaban monotherapy, as compared with combination therapy, for the primary efficacy endpoint. ● Cox proportional-hazards model was used to compare outcomes between the two groups, with the results expressed as a hazard ratio with a 95% confidence interval. ● A one-sided alpha level of 0.025 to analyze the noninferiority of rivaroxaban monotherapy, as compared with combination therapy, with a noninferiority margin of 1.46. ● Primary & secondary efficacy analysis performed with modified intent-to-treat approach
Results	
Enrollment	● 2236 Underwent Randomization o 1118 → Monotherapy Group ▪ 1107 included in the modified intention to treat analysis ● 1099 included in the safety analysis o 1084 included in the per protocol analysis ▪ 1005 completed trial follow-up o 1118 → Combination Group ▪ 1108 included in the modified intention to treat analysis ● 1099 included in the safety analysis o 1075 included in the per protocol analysis ▪ 968 completed trial follow-up Patients were randomly assigned in a 1:1 ratio to receive monotherapy with rivaroxaban or combination therapy with rivaroxaban plus an antiplatelet agent (either aspirin or a P2Y12 inhibitor) Randomization was performed after adjustment for the following factors with the use of a minimization algorithm: age, sex, history of percutaneous coronary intervention, history of stroke, concomitant heart failure, hypertension, and diabetes mellitus

Baseline Characteristics

Table 1. Characteristics of the Patients at Baseline (Modified Intention-to-Treat Population).*

Characteristic	Rivaroxaban Monotherapy (N=1107)	Combination Therapy (N=1108)
Age — yr	74.3±8.3	74.4±8.2
<75 yr — no. (%)	525 (47.4)	527 (47.6)
≥75 yr — no. (%)	582 (52.6)	581 (52.4)
Male sex — no. (%)	875 (79.0)	876 (79.1)
Body-mass index†	24.5±3.7	24.5±3.7
Current smoker — no. (%)	146 (13.2)	146 (13.2)
Diabetes — no. (%)	461 (41.6)	466 (42.1)
Previous stroke — no. (%)	148 (13.4)	175 (15.8)
Previous myocardial infarction — no. (%)	384 (34.7)	393 (35.5)
Previous PCI — no. (%)	781 (70.6)	783 (70.7)
Type of stent — no./total no. (%)		
Drug-eluting	500/723 (69.2)	477/721 (66.2)
Bare-metal	171/723 (23.7)	171/721 (23.7)
Both types	19/723 (2.6)	36/721 (5.0)
Unknown	33/723 (4.6)	37/721 (5.1)
Previous CABG — no. (%)	125 (11.3)	127 (11.5)
Type of atrial fibrillation — no. (%)		
Paroxysmal	596 (53.8)	580 (52.3)
Persistent	164 (14.8)	175 (15.8)
Permanent	347 (31.3)	353 (31.9)
Creatinine clearance		
Mean — ml/min	62.8±25.7	61.7±24.0
Distribution — no./total no. (%)		
<30 ml/min	54/1053 (5.1)	60/1039 (5.8)
30 to <50 ml/min	300/1053 (28.5)	293/1039 (28.2)
≥50 ml/min	699/1053 (66.4)	686/1039 (66.0)

Primary Results

Primary Results: Rivaroxaban Monotherapy vs Combination Therapy

- **Cardiovascular Events or Death from any cause**
  - 89 (4.14%) vs 121 (5.75%) [HR 0.72; 95% CI 0.55-0.95]

Primary Safety Endpoint: Rivaroxaban Monotherapy vs Combination Therapy

- **Major Bleeding**
  - 35 (1.62%) vs 58 (2.76%) [HR 0.59; 95% CI 0.39-0.89]

Secondary Results

Secondary Results: Rivaroxaban Monotherapy vs Combination Therapy

Cardiovascular Events

- Ischemic Stroke
  - 21 (0.96%) vs 28 (1.31%) [HR 0.73; 95% CI 0.42-1.29]
- Hemorrhagic Stroke
  - 4 (0.18%) vs 13 (0.60%) [HR 0.30; 95% CI 0.10-0.92]
- Myocardial Infarction
  - 13 (0.59%) vs 8 (0.37%) [HR 1.60; 95% CI 0.67-3.87]
- Unstable Angina Requiring Revascularization
  - 13 (0.59%) vs 18 (0.84%) [HR 0.71; 95% CI 0.35-1.44]
- Systemic Embolism
  - 2 (0.09%) vs 1 (0.05%) [HR 1.97; 95% CI 0.18-21.73]

Death

- Cardiovascular
  - 26 (1.17%) vs 43 (1.99%) [HR 0.59; 95% CI 0.36-0.96]
- Non-Cardiovascular
  - 15 (0.68%) vs 30 (1.39%) [HR 0.49; 95% CI 0.27-0.92]

Author's Conclusions

Among patients with atrial fibrillation and stable coronary artery disease, rivaroxaban monotherapy vs. rivaroxaban/antiplatelet therapy was **noninferior for ischemia and superior for bleeding**

Overall Critique and Discussion of Findings and Clinical Relevance	
Strengths	● Large sample size ● Patients randomized evenly in a 1:1 ratio
Limitations	● Open Label Design - potential to introduce observer bias o Countermeasure → All the events for which medical attention was sought were adjudicated by the members of an independent committee who were unaware of trial-group assignments. ● Relatively high rates of withdrawal of consent and loss of patients to follow-up o Still within the 5% anticipated rate of discontinuation & was consistent between the 2 groups ● Trial population received rivaroxaban dose approved in Japan (10 mg or 15 mg daily, according to the patient's CrCl) instead of globally approved 20mg once-daily dose. o Rivaroxaban serum level in blood samples from Japanese patients taking lower rivaroxaban 15-mg dose was similar to serum level of white patients taking 20-mg dose ● The low dose of prasugrel 3.75mg used in the trial brings uncertainty regarding possible increased risk of bleeding while not providing a meaningful effect on reducing thrombotic risk. ● The choice of antiplatelet regimen was at the discretion of the treating physicians o This makes it uncertain whether the benefit of rivaroxaban monotherapy applies equally to the two combination regimens. ● Women represented only about 20% of the study population, which makes it uncertain if the results of this study can be generalized to the female population particularly as that population presents a higher CHA2DS2-VASc score and is therefore at greater risk of stroke. ● The study population consisted entirely of individuals from Osaka, Japan which leads to uncertainty regarding the generalizability of the study results to populations in other areas of the world.
Discussion	● Unlike OAC-ALONE, the AFIRE trial was able to complete enrollment with sufficient power to examine non-VKA oral anticoagulation monotherapy ● The trial met its primary objective to demonstrate noninferiority of Rivaroxaban monotherapy compared to Rivaroxaban + antiplatelet therapy for composite of CV events or deaths from any cause. ● This randomized clinical trial provides evidence to support the approach of using non-VKA oral anticoagulant monotherapy in AF patients beyond 1 year post-PCI/Angiography on the basis of superior safety, and non-inferior efficacy.
Your Conclusions	In patients with AF in the setting of stable ACS 1 year post-revascularization or angiographically confirmed ACS, it is reasonable to continue Rivaroxaban monotherapy without concurrent Antiplatelet therapy due to evidence indicating that monotherapy offers a reduction in risk of bleed, without any significant increase in ischemic risks.

References

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Appendix

CAD	Coronary Artery Disease
CAG	Coronary Angiography
CABG	Coronary Artery Bypass Graft
POBA	Plain Old Balloon Angioplasty
PCI	Percutaneous Coronary Intervention
CrCl	Creatinine Clearance
MI	Myocardial Infarction
TIA	Transient Ischemic Attack
VTE	Venous Thromboembolism
OAC	Oral Anticoagulant
RCT	Randomized Control Trial

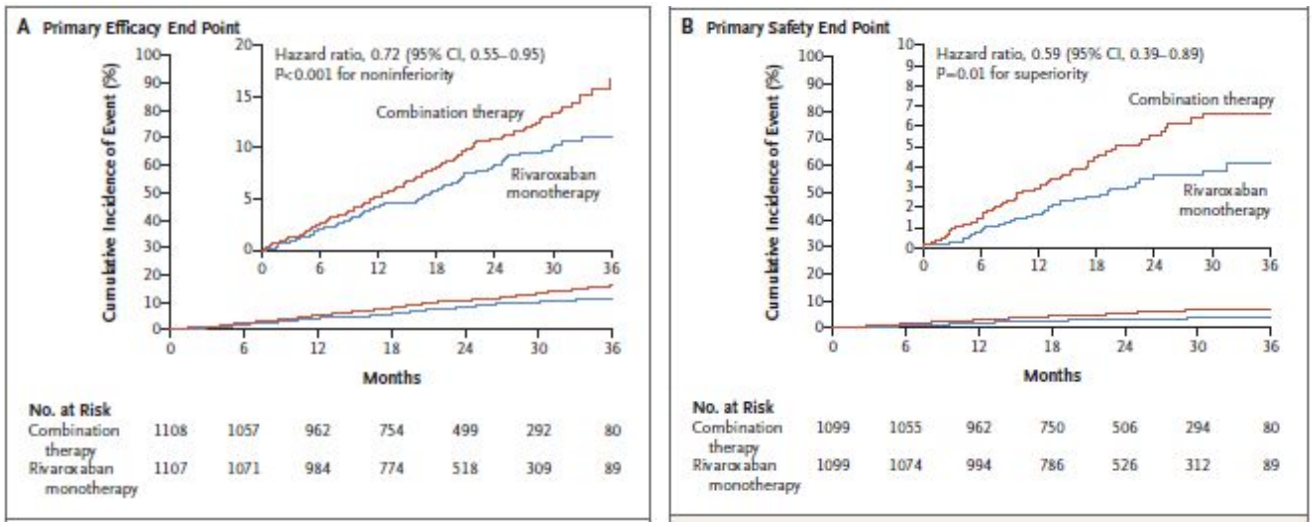

Figure 2. Primary Efficacy and Safety End Points.
Panel A shows the primary efficacy end point — a composite of stroke, systemic embolism, myocardial infarction, unstable angina requiring revascularization, or death from any cause — in the monotherapy group and the combination-therapy group. Panel B shows the primary safety end point of major bleeding, as defined by the criteria of the International Society on Thrombosis and Hemostasis. The inset graphs show the same data on an expanded y axis.

- For 80% power
  - n=1011 per arm to verify noninferiority in primary efficacy endpoint based on 6.10% incidence of CV events in the ROCKET-AF trial.
  - n=1099 per arm to verify superiority in primary safety endpoint based on bleeding frequency in ROCKET-AF trial (3.23% rivaroxaban, 5.05% rivaroxaban+ASA)
  - Average 2 year follow-up (Max. observation period 3yr, 5% dropout rate