

SHORT COMMUNICATION

OPEN ACCESS

Aspirin Plus Oral Anticoagulation in High-Risk Patients with Stable Coronary Artery Disease After Percutaneous Coronary Intervention Stenting: Important Lessons Learned from the AQUATIC Trial

Elfreda Dzukey¹  Kevan English² 

¹ Department of Pharmacy, Campbell University College of Pharmacy & Health Sciences, Buies Creek, NC, USA

² Department of Internal Medicine, University of Nebraska Medical Center, Omaha, NE, USA

Antithrombotic treatment in patients with stable coronary artery disease and previous stent implantation who require long-term oral anticoagulation is a constant challenge in clinical practice, especially for patients who are at high risk for vascular and coronary events. Stopping aspirin in high-risk patients with chronic coronary syndrome after percutaneous coronary intervention may lead to recurrent ischemic events, whereas combination therapy with aspirin and oral anticoagulation may lead to a higher risk of bleeding. For decades, we thought the answer of combination therapy was superior to anticoagulation monotherapy. However, several clinical trials have shown evidence against this practice. This short communication provides an in-depth analysis of the AQUATIC clinical trial and its potential implications for the treatment of AF and CAD.

Keywords: Chronic coronary syndrome; aspirin; direct oral anticoagulants; clinical trial; coronary artery disease; percutaneous coronary intervention; warfarin

The Assessment of Quitting versus Using Aspirin Therapy in Patients with Stabilized Coronary Artery Disease (CAD) after Stenting Who Require Long-Term Oral Anticoagulation (AQUATIC) trial was a prospective, randomized, double-blind, placebo-controlled, parallel group, multicenter study conducted in France that studied the addition of low-dose aspirin (ASA) to oral anticoagulation (OAC) in patients

with an anticoagulation indication (i.e., atrial fibrillation [AF]) and a chronic coronary syndrome, formerly known as stable CAD (1). The combination of these two therapies is common in North American clinical practice and commonly occurs in two ways. The first way includes a patient who develops AF, then subsequently gets diagnosed with CAD by some diagnostic modality, prompting ASA

Corresponding Author: Kevan English, MD; Department of Internal Medicine, University of Nebraska Medical Center, Omaha, NE, USA

E-mail: keenglish@unmc.edu

ORCID: 0009-0006-8893-5696

Received: Jan 3, 2026 **Accepted:** March 5, 2026

Published: March 26, 2026

This is an Open Access article distributed under the terms of Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, or reproduction in any area, original work is properly cited.

The Ulutas Medical Journal © 2026



therapy. The other way includes a patient who has been on ASA for years and develops AF, prompting OAC. The theory behind this practice is that the OAC treats the AF in patients who meet criteria, and the ASA covers the chronic coronary syndrome. Several trials published over the last decade have shown a high bleeding risk with dual-pathway therapy with a single antiplatelet agent and full-dose OAC than with OAC alone (2-5). However, these studies were open-label and included low-risk patients, and ultimately had little effect on the common practice of using both agents.

In the trial, the investigators randomized 872 patients to receive ASA (100 mg once daily) or a placebo. For inclusion, patients had to be high risk and have undergone a percutaneous coronary intervention more than 6 months prior to enrollment. The mean age of patients was 72 years, and more than 80% were male. 72.1% of patients had a history of myocardial infarction, and the median CHA₂DS₂-VASc score was 4 (interquartile range, 3.0 – 5.0). The primary efficacy outcome was a composite of cardiovascular death, stroke, myocardial infarction, coronary revascularization, acute limb ischemia, or systemic embolism. The key safety endpoint was major bleeding, as defined by the International Society on Thrombosis and Hemostasis (ISTH) criteria. One would expect more bleeding events in the dual-therapy arm and fewer thrombotic events compared with placebo, which would be a logical conclusion. However, this did not occur. Instead, the trial had to be stopped prematurely because an interim analysis showed harm in the dual-therapy group.

The combination arm had a 53% higher rate of the primary efficacy endpoint (95% confidence interval [CI], 1.07–2.18), with a P value of 0.02. The bleeding outcome was even worse. Major bleeding occurred in 10.2% of patients in the ASA group and 3.4% in the placebo group (adjusted hazard ratio, 3.35;

95% CI, 1.87 to 6.00; $P < 0.001$). The authors conclude that the dual-therapy arm was evidently worse than single OAC therapy.

Overall, several key lessons can be taken away from this trial. First, the AQUATIC trial compares well with two previous trials (EPIC CAD and AFIRE), which also found worse outcomes with combination therapy from a bleeding standpoint (2,4). In the EPIC CAD trial, major bleeding or clinically relevant nonmajor bleeding occurred in 23 patients (4.7%) in the edoxaban monotherapy group and in 70 patients (14.2 %) in the combination group (hazard ratio, 0.34; 95%CI, 0.22 to 0.53). Similarly, the AFIRE trial reported a lower incidence of nonmajor bleeding events in patients receiving monotherapy than those receiving combination therapy (hazard ratio, 0.58; 95%CI, 0.46 to 0.72). When similar trials find comparable results, medical community tends to be more accepting, and we become more confident in the findings. This trial showed an increase in thrombotic events in the combination arm, unlike previous trials. This finding is unique among the others and prompts us to think more. Patients were notably enrolled from May 2020 through April 2024. Perhaps the COVID-19 pandemic contributed to the observed findings. A second lesson to take away from the article is that there is little uncertainty here. The absolute difference in the primary outcome (16.9% vs 12.1%) is 4.8%, translating to a number needed to harm of just 21. From a bleeding standpoint, the absolute risk increase was 6.8% (10.2% vs 3.4%), translating to a number needed to harm of only 15. These results signify worsening bleeding outcomes in the combination group. Lastly, the authors showed that clinical questions can be answered with proper trials. Clinical studies are often designed to yield positive results for a profitable new therapy. However, this trial clearly showed that dual therapy causes more harm than good.

For decades, we assumed that patients with both AF and CAD required separate agents. However, findings from recent clinical studies, most notably the AQUATIC trial, have shown that we were wrong. With the ongoing emergence of data on combination therapy for AF and CAD, we recommend that the medical community remain open to OAC monotherapy when both diseases are present. Some places in Europe have begun implementing this practice.

Conflict of Interest

The authors declare no relevant conflicts of interest for this article. None of the authors received any financial grant that could be considered a potential conflict of interest regarding this manuscript or its submission.

Author Contributions

Dzukey wrote the original draft, contributed to conceptualization, writing, reviewing, and editing. English reviewed and edited the article. All authors read and approved the final version of the manuscript.

References

1. Lemesle G, Didier R, Steg PG, Simon T, Montalescot G, Danchin N, Bauters C, Blanchard D, Bouleti C, Angoulvant D, Andrieu S, Vanzetto G, Kerneis M, Decalf V, Puymirat E, Mottier D, Diallo A, Vicaut E, Gilard M, Cayla G; AQUATIC Trial Investigators. Aspirin in Patients with Chronic Coronary Syndrome Receiving Oral Anticoagulation. *N Engl J Med*. 2025 Oct 23;393(16):1578-1588
2. Cho MS, Kang DY, Ahn JM, Yun SC, Oh YS, Lee CH, Choi EK, Lee JH, Kwon CH, Park GM, Choi HO, Park KH, Park KM, Hwang J, Yoo KD, Cho YR, Kim JH, Hwang KW, Jin ES, Kwon O, Kim KH, Park SJ, Park DW, Nam GB; EPIC-CAD Investigators. Edoxaban Antithrombotic Therapy for Atrial Fibrillation and Stable Coronary Artery Disease. *N Engl J Med*. 2024 Dec 5;391(22):2075-2086
3. Matsumura-Nakano Y, Shizuta S, Komasa A, Morimoto T, Masuda H, Shiomi H, Goto K, Nakai K, Ogawa H, Kobori A, Kono Y, Kaitani K, Suwa S, Aoyama T, Takahashi M, Sasaki Y, Onishi Y, Mano T, Matsuda M, Motooka M, Tomita H, Inoko M, Wakeyama T, Hagiwara N, Tanabe K, Akao M, Miyauchi K, Yajima J, Hanaoka K, Morino Y, Ando K, Furukawa Y, Nakagawa Y, Nakao K, Kozuma K, Kadota K, Kimura K, Kawai K, Ueno T, Okumura K, Kimura T; OAC-ALONE Study

Investigators. 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 Jan 29;139(5):604-616

4. Yasuda S, Kaikita K, Akao M, Ako J, Matoba T, Nakamura M, Miyauchi K, Hagiwara N, Kimura K, Hirayama A, Matsui K, Ogawa H; AFIRE Investigators. Antithrombotic Therapy for Atrial Fibrillation with Stable Coronary Disease. *N Engl J Med*. 2019 Sep 19;381(12):1103-1113. doi: 10.1056/NEJMoa1904143. Epub 2019 Sep 2. Erratum in: *N Engl J Med*. 2021 Oct 21;385(17):1632
5. Fukamachi D, Okumura Y, Matsumoto N, Tachibana E, Oiwa K, Ichikawa M, Haruta H, Nomoto K, Arima K, Hirayama A. Edoxaban Monotherapy in Nonvalvular Atrial Fibrillation Patients with Coronary Artery Disease. *J Interv Cardiol*. 2022 Dec 17;2022:5905022

Contact Details

Elfreda Dzukey, PharmD, MBA

Department of Pharmacy, Campbell
University College of Pharmacy & Health
Sciences, Buies Creek, Nebraska, United States
E-mail: eadzukey0813@email.campbell.edu

Kevan English, MD

Department of Internal Medicine
University of Nebraska Medical Center
Nebraska, United States
ORCID: 0009-0006-8893-5696
Mobile: 1-754-234-1993
E-mail: keenglish@unmc.edu

How to cite?

Elfreda Dzukey and Kevan English. Aspirin Plus Oral Anticoagulation in High-Risk Patients with Stable Coronary Artery Disease After Percutaneous Coronary Intervention Stenting: Important Lessons Learned from the AQUATIC Trial. *Ulutas Med J*. 2026;12(1):4-6

Doi: 10.5455/umj.20260104053745