

Dropping P2Y₁₂ inhibitors in patients with AF undergoing PCI? Not yet a SAFE bet



Renato D. Lopes^{1*}, MD, PhD; Alexander C. Fanaroff², MD, MHS

1. Division of Cardiovascular Medicine and Duke Clinical Research Institute, Durham, NC, USA; 2. Penn Cardiovascular Outcomes, Quality and Evaluative Research Center, Leonard Davis Institute, and Cardiovascular Medicine Division, University of Pennsylvania, Philadelphia, PA, USA

Up to 15% of patients with atrial fibrillation (AF) will ultimately undergo percutaneous coronary intervention (PCI) or have acute coronary syndrome¹. Management of these patients is challenging: long-term treatment with an oral anticoagulant (OAC) is necessary to prevent stroke and systemic embolisation related to AF, but dual antiplatelet therapy with aspirin plus a P2Y₁₂ inhibitor represents the standard of care to prevent stent thrombosis and recurrent myocardial infarction. The rate of major bleeding in patients treated with triple antithrombotic therapy (OAC plus aspirin plus a P2Y₁₂ inhibitor) approaches 10% per year, a rate twofold to threefold higher than that of patients treated with OAC alone². Despite the high bleeding risk associated with triple antithrombotic therapy, for a long time there was limited evidence supporting alternative strategies for managing these patients. Recently, four randomised controlled trials have compared double antithrombotic regimens including a non-vitamin K antagonist oral anticoagulant (NOAC) plus a P2Y₁₂ inhibitor (without aspirin) against triple antithrombotic therapy³⁻⁶. A meta-analysis of these trials showed that these

double antithrombotic therapy regimens reduce the risk of bleeding compared with triple antithrombotic therapy while maintaining efficacy for the prevention of ischaemic events⁷.

However, there are nearly limitless ways to combine the available OACs plus P2Y₁₂ inhibitors plus aspirin. Among the alternatives to double antithrombotic therapy with an OAC plus P2Y₁₂ inhibitor are regimens that drop the P2Y₁₂ inhibitor after a short duration in favour of an OAC plus aspirin. The type of regimen was tested in the ISAR-TRIPLE (Triple Therapy in Patients on Oral Anticoagulation After Drug Eluting Stent Implantation) trial, which randomised 614 patients with an indication for OAC undergoing PCI to warfarin plus aspirin plus either six weeks or six months of therapy with the P2Y₁₂ inhibitor clopidogrel. In that study, the authors found no difference in the primary composite outcome, a combination of ischaemic events and Thrombolysis In Myocardial Infarction (TIMI) major bleeding, which occurred in 9.8% of patients in the six-week clopidogrel group and 8.8% of patients in the six-month group. ISAR-TRIPLE was a small trial,

*Corresponding author: Duke Clinical Research Institute, P.O. Box 17969, Durham, NC 27715, USA.

E-mail: renato.lopes@duke.edu

powered only to detect a 60% reduction in events. Moreover, it enrolled patients between 2008 and 2013, before the availability of all NOACs and more potent P2Y₁₂ inhibitors; its warfarin-based regimen is less relevant in the NOAC era.

The SAFE-A (Short-duration triple antithrombotic therapy for atrial fibrillation patients who require coronary stenting) trial, published in this edition of EuroIntervention⁸, builds on the design of ISAR-TRIPLE.

Article, see page 164

SAFE-A randomised patients with AF undergoing PCI to either one month or six months of P2Y₁₂ inhibitor therapy (clopidogrel or prasugrel) on a background of apixaban plus aspirin. The authors intended to enrol 600 patients, giving them 80% power to detect a 50% reduction in the primary outcome of any bleeding, but the trial was stopped early due to slow recruitment after 210 patients were enrolled. The primary endpoint occurred in 12/102 patients in the one-month P2Y₁₂ inhibitor arm and 17/106 patients in the six-month P2Y₁₂ inhibitor arm (11.8 vs 16.0%; hazard ratio [HR] 0.70, 95% confidence interval [CI]: 0.33-1.47). Ten patients in the one-month arm had an ischaemic event (death, myocardial infarction, stroke, or systemic embolism) compared with three in the six-month arm (9.8 vs 2.8%; HR 3.00, 95% CI: 0.82-10.94).

The SAFE-A approach to antithrombotic therapy is worthy of consideration. Despite the results of clinical trials, many PCI operators remain concerned that dropping aspirin following PCI increases the risk of stent thrombosis. Stent thrombosis is rare enough that clinical trials have not been powered to detect a change in its incidence with less aggressive antithrombotic therapy, but it can be very serious or fatal to individual patients. The great majority of stent thrombosis events occur in the first month after PCI⁹, and one month of P2Y₁₂ inhibitor therapy appears safe in high-bleeding risk patients undergoing PCI with third-generation drug-eluting stents¹⁰, providing rationale for a strategy that employs a short duration of triple antithrombotic therapy. After the first month, whether single antiplatelet therapy with aspirin or a P2Y₁₂ inhibitor provides

the optimal balance of protection from ischaemic events and bleeding events has not been tested in randomised controlled trials. However, though the rate of bleeding and ischaemic events in SAFE-A is similar to that in other trials evaluating double antithrombotic therapy regimens (**Figure 1**), SAFE-A has several limitations that make its interpretation challenging. It was stopped early with one third of the intended sample size, and consequently had a small number of events. It enrolled patients in a single country and used a dose of prasugrel (3.75 mg daily) that is not available in most parts of the world. It used a bleeding definition that combined different bleeding scales and different bleeding severities, which is not typical for other trials in this area and is difficult to interpret.

For these reasons, the SAFE-A trial is unable to inform physicians how to treat patients with AF and PCI. Until we have an appropriately powered trial testing the SAFE-A regimen, physicians should use a NOAC plus a P2Y₁₂ inhibitor for patients with AF undergoing PCI. This has been shown in four appropriately powered trials to represent the antithrombotic sweet spot in the prevention of ischaemic events at a minimal cost of bleeding events in this high-risk, challenging population.

Conflict of interest statement

R. Lopes reports research grants from Bristol-Myers Squibb, GlaxoSmithKline, Medtronic, Pfizer, and Sanofi; and personal fees from Amgen, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Medtronic, Pfizer, and Sanofi. A. Fanaroff reports a career development grant from the American Heart Association, grant funding from Boston Scientific, and honoraria from the American Heart Association.

References

1. Capodanno D, Huber K, Mehran R, Lip GYH, Faxon DP, Granger CB, Vranckx P, Lopes RD, Montalescot G, Cannon CP, Ten Berg J, Gersh BJ, Bhatt DL, Angiolillo DJ. Management of Antithrombotic Therapy in Atrial Fibrillation Patients Undergoing PCI: JACC State-of-the-Art Review. *J Am Coll Cardiol*. 2019;74:83-99.

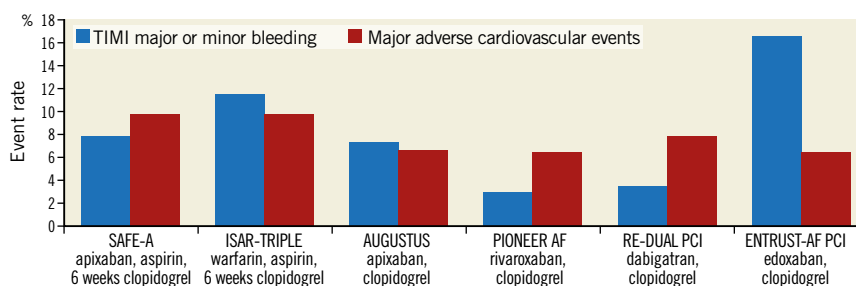


Figure 1. Ischaemic and major bleeding events in the double antithrombotic therapy arms of clinical trials enrolling patients with atrial fibrillation and either acute coronary syndrome or undergoing percutaneous coronary intervention. Rates of bleeding and major adverse cardiovascular events were relatively similar in the double antithrombotic arms of all trials. Major adverse cardiovascular events include all-cause or cardiovascular death, myocardial infarction, and stroke or systemic embolism. TIMI major and minor bleeding was selected for display as it was the only bleeding outcome reported by all trials. WOEST did not report the composite of death, myocardial infarction, and stroke or systemic embolism and is not included.

2. van Rein N, Heide-Jørgensen U, Lijfering WM, Dekkers OM, Sørensen HT, Cannegieter SC. Major Bleeding Rates in Atrial Fibrillation Patients on Single, Dual, or Triple Antithrombotic Therapy. *Circulation*. 2019;139:775-86.
3. Gibson CM, Mehran R, Bode C, Halperin J, Verheugt FW, Wildgoose P, Birmingham M, Ianus J, Burton P, van Eickels M, Korjian S, Daaboul Y, Lip GY, Cohen M, Husted S, Peterson ED, Fox KA. Prevention of bleeding in patients with atrial fibrillation undergoing PCI. *N Engl J Med*. 2016;375:2423-34.
4. Lopes RD, Heizer G, Aronson R, Vora AN, Massaro T, Mehran R, Goodman SG, Windecker S, Darius H, Li J, Averkov O, Bahit MC, Berwanger O, Budaj A, Hijazi Z, Parkhomenko A, Sinnaeve P, Storey RF, Thiele H, Vinereanu D, Granger CB, Alexander JH; AUGUSTUS Investigators. Antithrombotic Therapy after Acute Coronary Syndrome or PCI in Atrial Fibrillation. *N Engl J Med*. 2019;380:1509-24.
5. Cannon CP, Bhatt DL, Oldgren J, Lip GYH, Ellis SG, Kimura T, Maeng M, Merkely B, Zeymer U, Gropper S, Nordaby M, Kleine E, Harper R, Manassie J, Januzzi JL, Ten Berg JM, Steg PG, Hohnloser SH; RE-DUAL PCI Steering Committee and Investigators. Dual antithrombotic therapy with dabigatran after PCI in atrial fibrillation. *N Engl J Med*. 2017;377:1513-24.
6. Vranckx P, Valgimigli M, Eckardt L, Tijssen J, Lewalter T, Gargiulo G, Batushkin V, Campo G, Lysak Z, Vakaliuk I, Milewski K, Laeis P, Reimitz PE, Smolnik R, Zierhut W, Goette A. Edoxaban-based versus vitamin K antagonist-based antithrombotic regimen after successful coronary stenting in patients with atrial fibrillation (ENTRUST-AF PCI): a randomised, open-label, phase 3b trial. *Lancet*. 2019;394:1335-43.
7. Lopes RD, Hong H, Harskamp RE, Bhatt DL, Mehran R, Cannon CP, Granger CB, Verheugt FWA, Li J, Ten Berg JM, Sarafoff N, Vranckx P, Goette A, Gibson CM, Alexander JH. Optimal Antithrombotic Regimens for Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention: An Updated Network Meta-analysis. *JAMA Cardiol*. 2020 Feb 26. [Epub ahead of print].
8. Hoshi T, Sato A, Hiraya D, Watbe H, Takeyasu N, Ohigashi T, Gosho M, Ieda M, Aonuma K. Short-duration triple antithrombotic therapy for atrial fibrillation patients who require coronary stenting: results of the SAFE-A study. *EuroIntervention*. 2020;16:e164-72.
9. Lopes RD, Leonardi S, Wojdyla DM, Vora AN, Thomas L, Storey RF, Vinereanu D, Granger CB, Goodman SG, Aronson R, Windecker S, Thiele H, Valgimigli M, Mehran R, Alexander JH. Stent Thrombosis in Patients With Atrial Fibrillation Undergoing Coronary Stenting in the AUGUSTUS Trial. *Circulation*. 2020;141:781-3.
10. Windecker S, Latib A, Kedhi E, Kirtane AJ, Kandzari DE, Mehran R, Price MJ, Abizaid A, Simon DI, Worthley SG, Zaman A, Hudec M, Poliacikova P, Abdul Ghapar AKB, Selvaraj K, Petrov I, Mylotte D, Pinar E, Moreno R, Fabbiochi F, Pasupati S, Kim HS, Aminian A, Tie C, Wlodarczak A, Hur SH, Marx SO, Jankovic I, Brar S, Bousquette L, Liu M, Stone GW; ONYX ONE Investigators. Polymer-based or Polymer-free Stents in Patients at High Bleeding Risk. *N Engl J Med*. 2020;382:1208-18.