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Commentary

Navigating the treacherous waters of antithrombotic therapies in patients with atrial fibrillation and coronary artery disease: Lessons from AUGUSTUS

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Determining the optimal antithrombotic regimen to prevent ischemic events and bleeding presents a challenge to cardiologists in managing their patients with atrial fibrillation (AF) who experience an acute coronary syndrome (ACS) and/or undergo percutaneous coronary intervention (PCI). The general consensus is to continue oral anticoagulation (OAC) to prevent stroke and to modify antiplatelet intensity and/or duration to minimize bleeding; however, the optimal combination has yet to be identified [1,2]. The most common reason to use a strategy of OAC plus a P2Y12-inhibitor plus aspirin is the perception that this regimen reduces the risk of ischemic events, including stent thrombosis. The risk of stent thrombosis, a rare and frequently fatal complication, is higher in the first weeks following PCI prior to re-endothelialization of the stent struts and/or polymer material, and is of particular concern when PCI occurs in the prothrombotic setting of ACS [3,4]. Over the past decade a number of randomized controlled trials, of which AUGUSTUS is the latest, have challenged the axiom that a combination of OAC plus dual antiplatelet therapy is required in all patients [5].

In AUGUSTUS, 4614 patients with AF and ACS and/or PCI were randomized in a 2-by-2 fashion to apixaban or a vitamin K antagonist (VKA) and aspirin or placebo for a duration of 6 months. All patients were taking a P2Y12-inhibitor, which was clopidogrel in > 90% of participants. The median time from the index event to randomization was 6 days. The trial met its primary endpoint, major or clinically relevant non-major bleeding, which was lower in the group receiving apixaban compared with those receiving VKA (10.5% vs. 14.7%; hazard ratio [HR] 0.69, 95% confidence interval [CI] 0.58–0.81) and those receiving aspirin compared with placebo (16.1% vs. 9.0%; HR 1.89, 95% CI 1.59–2.24). The trial's secondary endpoint of death or hospitalization was also lower with apixaban compared with VKA (23.5% vs. 27.4%; HR 0.83, 95% CI 0.74–0.93) and comparable between aspirin and placebo. There was no significant difference, either between apixaban and VKA or between aspirin and placebo, in major adverse cardiovascular events (MACE).

In this issue of the *Journal*, Andrea Rubboli [6] points out that there is not so much debate on the choice of OAC, but the central question is what to do with aspirin. In principle, Dr. Rubboli is right; the findings of AUGUSTUS, while compelling, did not exclude a modest and potentially clinically significant increase in MACE, and certainly did not exclude potential increases in individual ischemic events such as stent thrombosis. However, the results of the antiplatelet comparison in AUGUSTUS must be considered in total. We learned that omitting aspirin results in a large (47%) reduction in bleeding. The overall rate of ischemic events was low, particularly the rate of stent thrombosis—only 32 (0.7%) patients in the entire study had definite or probable stent thrombosis. In patients assigned to aspirin, stent thrombosis occurred in 0.5% compared with 0.9% in patients assigned to placebo. Therefore continuing aspirin decreased stent thrombosis by an absolute 0.4%. The number needed to treat to prevent 1 case of stent thrombosis over 6 months with aspirin is around 250, and comes at the cost of around 18 additional major or clinically relevant non-major bleeding events. This is the new finding from the antiplatelet comparison in AUGUSTUS; we now know the cost to pay in terms of bleeding if one decides to use aspirin for 6 months to prevent stent thrombosis. Based on this, for the majority of patients, aspirin can be safely discontinued after initial treatment of the ACS/PCI event. In practical terms: all patients with ACS/PCI should also receive aspirin as their initial treatment for at least a few days, which in most cases equals the time of hospitalization, with aspirin discontinued around hospital discharge. However, there are still questions to be answered about timing, predictors, and prognosis of stent thrombosis as well as the risk-benefit ratio between stent thrombosis and bleeding at different time points after the ACS/PCI event. Additional analyses from AUGUSTUS may provide some answers to help physicians further tailor the duration of aspirin for these patients allowing a more personalized approach to antiplatelet therapy after PCI.

Dr. Rubboli suggests that the superior safety found with apixaban over VKA is likely a class effect of all non-VKA OACs (NOACs). This is clearly not the case in patients with AF without ACS/PCI, where different NOACs showed different results in terms of efficacy and safety when compared with warfarin [7–10]. Since different doses of different NOACs were tested in different trial designs in the setting of AF with ACS/PCI, a comparison across NOACs is not possible and thus inappropriate [5,11,12].

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The majority of guidelines recommendations in cardiology are based on low levels of evidence [13]. The field of anticoagulant and antiplatelet therapy for AF and ACS/PCI is a good example of this. For instance, if we consider a rare complication such as stent thrombosis, it is unlikely that there will be a definite conclusion on this topic any time in the foreseeable future, as it would necessitate a randomized clinical trial with tens of thousands of patients, which is an unrealistic prospect. Thus, if a very large trial needs to be conducted to potentially detect a difference between aspirin and placebo on a rare event such as stent thrombosis, perhaps this difference might not be relevant in light of the real and high risk of bleeding associated with aspirin use.

What can we learn from the current state of evidence in the field? At this stage, it is simply guesswork to conclude that any duration of add-on aspirin therapy would be of benefit. The duration could be anything from days to weeks or even longer. In AUGUSTUS the average time to randomization was 6 days. Prior to these 6 days patients were often treated with aspirin. Thus, one reasonable approach is to use aspirin during the initial treatment of the ACS/PCI event and during the course of hospitalization. Aspirin can then be safely discontinued around the time of discharge and the OAC and P2Y12-inhibitor maintained for at least 6 months. AUGUSTUS shows that in a field of little solid evidence and lots of opinions, less might be more. The use of better combinations of antithrombotic agents can lead to a more favorable net clinical benefit in this high-risk group of patients with AF and ACS/PCI.

Declaration of competing interests

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References

[1] January CT, Wann LS, Calikins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation. Circulation 2019. https://doi.org/10.1161/CIR.0000000000000665. epublication ahead of print.

[2] 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.

[3] Claessen BE, Henriques JPS, Jaffer FA, Mehran R, Piek JJ, Dangas GD. Stent thrombosis: a clinical perspective. JACC Cardiovasc Interv 2014;7:1081–92.

[4] Aoki J, Lansky AJ, Mehran R, et al. Early stent thrombosis in patients with acute coronary syndromes treated with drug-eluting and bare metal stents: the acute catheterization and urgent intervention triage strategy trial. Circulation 2009;119:687–98.

[5] Lopes RD, Heizer G, Aronson R, et al. Antithrombotic therapy after acute coronary syndrome or PCI in atrial fibrillation. N Engl J Med 2019;380:1509–24.

[6] Rubboli A. And now we have the AUGUSTUS–how will it impact on antithrombotic therapy in patients with atrial fibrillation undergoing percutaneous coronary intervention? Eur J Intern Med 2019. [in press].

[7] Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361:1139–51.

[8] Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;365:883–91.

[9] Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011;365:981–92.

[10] Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2013;369:2093–104.

[11] Gibson CM, Mehran R, Bode C, et al. Prevention of bleeding in patients with atrial fibrillation undergoing PCI. N Engl J Med 2016;375:2423–34.

[12] Cannon CP, Bhatt DL, Oldgren J, et al. Dual antithrombotic therapy with dabigatran after PCI in atrial fibrillation. N Engl J Med 2017;377:1513–24.

[13] Fanaroff AC, Califf RM, Windecker S, Smith Jr. SC, Lopes RD. Levels of evidence supporting American College of Cardiology/American Heart Association and European Society of Cardiology Guidelines, 2008–2018. JAMA 2019;321:1069–80.