European Journal of Internal Medicine 65 (2019) 1–3

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Clinical Insights

And now we have the AUGUSTUS … How will it impact on antithrombotic therapy in patients with atrial fibrillation undergoing percutaneous coronary intervention?

Optimal antithrombotic therapy in patients with atrial fibrillation (AF) undergoing percutaneous coronary intervention with stent (PCI) should consist of both oral anticoagulation (OAC) and antiplatelet therapy to effectively prevent major adverse cerebral (stroke) and cardiac (death, myocardial infarction, urgent revascularization, and stent thrombosis) ischemic events (MACCE). While the so-called triple therapy with a vitamin K-antagonist (VKA), aspirin and clopidogrel has long been proposed as the default strategy [1], double therapy with a non-vitamin K-antagonist (NOAC) and clopidogrel has subsequently shown a more favorable net clinical effect, being associated with less bleeding events and no apparent increase in MACCE [2,3]. Which part of this result can be attributed to the type of OAC, i.e., NOAC vs. VKA, and which to the antithrombotic regimen, i.e., double vs. triple, remains to be determined.

The AUGUSTUS trial was designed to compare the incidence of bleeding events with the NOAC apixaban vs. VKA, and with double vs. triple therapy in patients with AF undergoing PCI or having an acute coronary syndrome [4]. A total of 4614 patients were enrolled in a prospective, multicentre, 2 × 2 factorial, randomized fashion, and followed up for 6 months [4]. The primary endpoint was major/clinically relevant non-major (CRNM) bleeding as defined by the International Society on Thrombosis and Hemostasis (ISTH), whereas the secondary endpoints included the composite of death/hospitalization and death/ischemic events (stroke, myocardial infarction, definite/probable stent thrombosis, or urgent revascularization) [4].

Upon comparison of OAC, use of apixaban was associated with significantly lower major/CRNM bleeding vs. VKA (10.5% vs. 14.7%; hazard ratio [HR] 0.69; 95% confidence interval [CI] 0.58–0.81; $p < .001$ for both non-inferiority and superiority) [4] (Fig. 1). Death/hospitalization was also significantly lower in patients receiving apixaban (23.5% vs. 27.4%; HR 0.83; 95% CI 0.74–0.93; $p = .002$), whereas death/ischemic events was comparable [4] (Fig. 1A). Of note, among the individual components of total ischemic events, stroke was reduced by 50% in the apixaban group (1.2% vs 2.4%; HR 0.50; 95% CI 0.26–0.97) [4]. Upon comparison of antithrombotic regimens, triple therapy was associated with significantly higher major/CRNM bleeding vs. double therapy (16.1% vs. 9.0%; HR 1.89; 95% CI 1.59–2.24; $p < .001$) (Fig. 1B) [4]. Death/hospitalization and death/ischemic events were comparable [4] (Fig. 1B). Of note, in the double therapy group the occurrence of definite/probable stent thrombosis, myocardial infarction and urgent revascularization was numerically, albeit not significantly, higher than in the triple therapy group [4].

Now, what are the implications for clinical practice of the results of the AUGUSTUS trial [4]? First, because of its superior safety apixaban should always be preferred to VKA when combined to (either single or dual) antiplatelet therapy. But based on the ARISTOTLE trial [5], shouldn't this be considered for any patient with AF, regardless of whether or not concomitant antiplatelet therapy is given? Because systematic switching from VKA to a NOAC is not considered sustainable in all healthcare systems, VKA therapy may likely be continued in AF patients, either without or with concomitant antiplatelet therapy (which needs however to be given only for as short as few weeks/months following PCI), provided that the quality of OAC is high, i.e., the time spent in the therapeutic range (TTR) is > 65–70% [6]. Whether apixaban should be preferred over the other NOACs following PCI is uncertain. No prospective data comparing dabigatran, rivaroxaban, and edoxaban to VKA, when combined with a same regimen of antiplatelet therapy, are available. Observations and considerations on dabigatran [7,8] suggest that the safety benefit over VKA reported with this NOAC in the RE-LY trial [9] in patients with non-valvular AF is maintained when antiplatelet therapy is given in conjunction. Superior safety over VKA appears to be a class effect of all NOACs, each of which when ongoing may therefore be confirmed for the few weeks/months of combined OAC and (either single or dual) antiplatelet therapy following PCI. Stronger consideration to apixaban may likely be given when a triple therapy regimen is chosen, given that it is the only NOAC being studied in such combination. Second, because of the insufficient power of the AUGUSTUS trial [4] to reliably detect differences in MACCE with double vs. triple therapy, as well as the signal of an increased risk of adverse ischemic cardiac events, including myocardial, infarction, stent thrombosis, and urgent revascularization with double therapy [4], the optimal antithrombotic regimen in AF patients undergoing PCI remains uncertain. It appears however, that an initial period of triple therapy should be granted to all patients. The question then, is for how long? In the AUGUSTUS trial [4] randomization was carried out a median of approximately 1 week following PCI, during which aspirin was given to all patients [4]. Because platelets are irreversibly inhibited by aspirin for their entire life, i.e., 7–10 days, and that at least 50% of inhibited platelets need to be replaced by new and functioning ones before effective hemostasis is re-established [10], it can be estimated that in the double therapy arm of the AUGUSTUS trial [4] the effect of initial (pre-randomization) triple therapy extended for approximately 1–2 weeks after PCI. Which may have not been enough. As may have not been enough in the RE-DUAL PCI trial [3], at least with the lower dose of dabigatran 110 mg twice daily, where an increase in myocardial infarction and stent thrombosis was observed with double therapy, after an overall (pre- and post-randomization) triple therapy effect of approximately 1 week. Thus, an initial period of few weeks, i.e., > 2 and likely at least 4 (to be possibly extended to

https://doi.org/10.1016/j.ejim.2019.05.019
Received 8 April 2019; Accepted 14 May 2019
Available online 23 May 2019

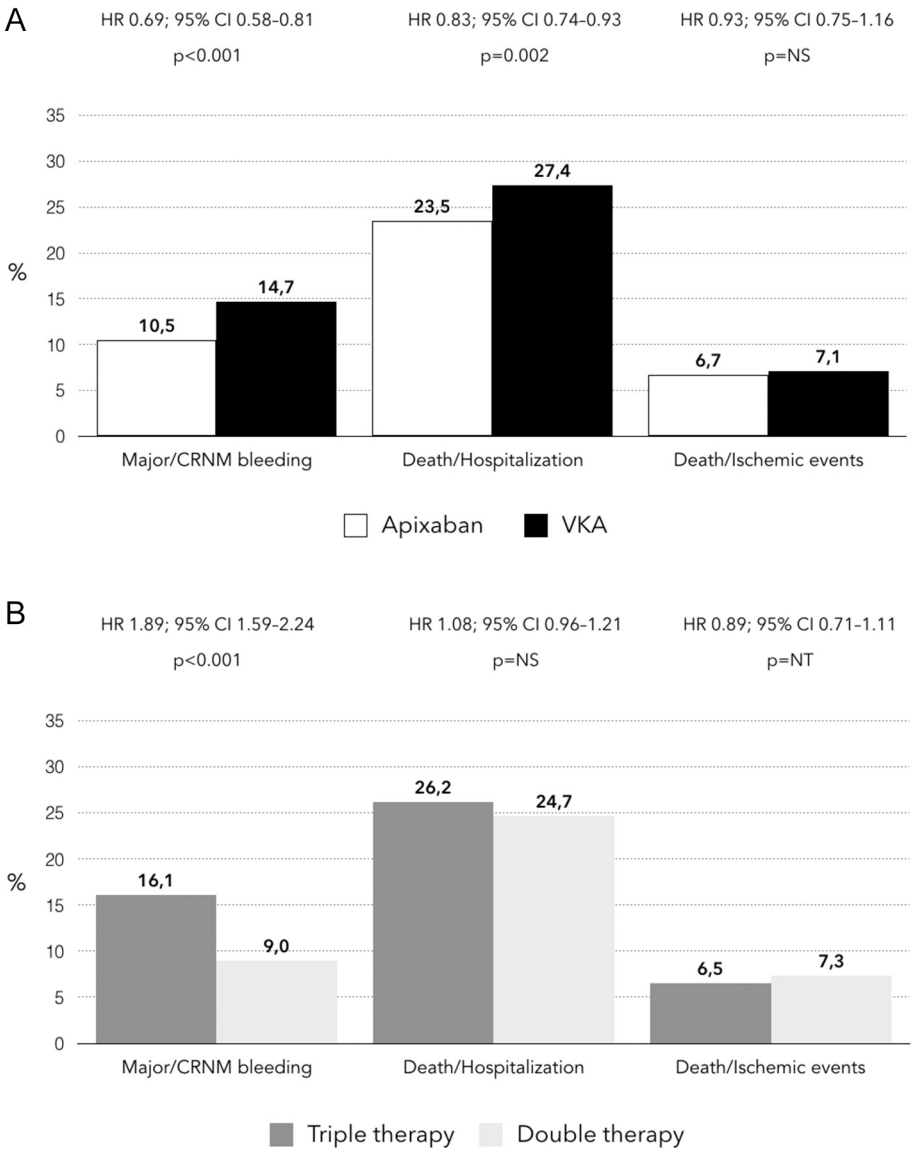

Fig. 1. Incidence of primary (safety) and secondary (efficacy) endpoints compared by: A) OAC (apixaban vs. VKA) and B) antithrombotic regimen (double vs. triple). OAC: oral anticoagulation, VKA: vitamin K antagonist, HR: hazard ratio, CI: confidence intervals, NS: not significant, NT: not tested.

12, unless the risk of bleeding is predominant), should be considered as the default strategy.

In conclusion, the AUGUSTUS trial [4] proved for the first time that in AF patients undergoing PCI a NOAC, namely apixaban, is significantly safer that VKA when combined to (either single or dual) antiplatelet therapy, so that it should generally be preferred as OAC. Instead, uncertainty persists on whether double and triple therapy are comparably effective, and actually some risk of increased ischemic cardiac events may be present with double therapy, so that, an initial course of triple therapy appears always indicated with its duration needing to be carefully individualized.

References

[1] Rubboli A, Halperin JL, Airaksinen KE, Buerke M, Eeckhout E, Freedman SB, et al. Antithrombotic therapy in patients treated with oral anticoagulation undergoing coronary artery stenting. An expert consensus document with focus on atrial fibrillation. Ann Med 2008;40:428–36.

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

[3] Cannon CP, Bhatt DL, Oldgren J, Lip GYH, Ellis SG, Kimura T, et al. Dual antithrombotic therapy with Dabigatran after PCI in atrial fibrillation. N Engl J Med 2017;377:1513–24.

[4] Lopes RD, Heizer G, Aronson R, Vora AN, Massaro T, Mehran R, et al. Antithrombotic therapy after acute coronary syndrome or PCI in atrial fibrillation. N Engl J Med Mar 17, 2019. https://doi.org/10.1056/NEJMoa1817083.

[5] Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011;365:981–92.

[6] Lip GYH, Collet JP, Haude M, Byrne R, Chung EH, Fauchier L, 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.

[7] Dans AL, Connolly SJ, Wallentin L, Yang S, Nakamya J, Brueckmann M, et al.

Concomitant use of antiplatelet therapy with dabigatran or warfarin in the randomized evaluation of long-term anticoagulation therapy (RE-LY) trial. Circulation 2013;127:634–40.
[8] Rubboli A. Superior safety of dual therapy with dabigatran and clopidogrel vs. triple therapy with warfarin, aspirin and clopidogrel in the RE-DUAL PCI trial: what is key, the strategy or the drug? Eur J Intern Med 2017;46:e40–1.
[9] Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361:1139–51.
[10] Angiolillo DJ, Ueno M, Goto S. Basic principles of platelet biology and clinical implications. Circ J 2010;74:597–607.

Andrea Rubboli*
Department of Cardiovascular Diseases - AUSL Romagna, Division of Cardiology, Ospedale S. Maria delle Croci, Ravenna, Italy
E-mail address: andrea.rubboli@auslromagna.it.

* Corresponding author at: Department of Cardiovascular Diseases - AUSL Romagna, Division of Cardiology, Ospedale S. Maria delle Croci, Viale Randi 5, 48121 Ravenna, Italy.