ALGORITHM FOR THE MANAGEMENT OF ANTITHROMBOTIC THERAPY IN ATRIAL FIBRILLATION PATIENTS UNDERGOING PERCUTANEOUS CORONARY INTERVENTION:

AN UPDATED PROPOSAL BASED ON EFFICACY CONSIDERATIONS.

Andrea Rubboli1, Gregory Y. H. Lip2

1 Department of Cardiovascular Diseases - AUSL Romagna, Division of Cardiology,

Ospedale S. Maria delle Croci, Viale Randi 5, 48121, Ravenna, Italy;

2 Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart & Chest Hospital, Liverpool, United Kingdom

*Short title*

ANTITHROMBOTIC THERAPY IN AF PATIENTS UNDERGOING PCI: AN UPDATED PROPOSAL

Address for correspondence:

Andrea Rubboli, MD, FESC

Department of Cardiovascular Diseases - AUSL Roma

Division of Cardiology, Ospedale S. Maria delle Croci

Viale Randi 5, 48121 Ravenna, Italy

Tel +390544285745, Fax +390544286756

Email andrearubboli@libero.it

KEY WORDS: atrial fibrillation, percutaneous coronary intervention, oral anticoagulation, non vitamin-K antagonist oral anticoagulant, warfarin

Following the publication of the results of the ENTRUST-AF PCI study (1), we now have prospective, randomized data on both safety and efficacy of a double antithrombotic regimen of a non-vitamin K-antagonist oral anticoagulant (NOAC), including apixaban, edoxaban, rivaroxaban, and dabigatran, and clopidogrel as compared to the conventional triple regimen of warfarin, aspirin, and clopidogrel, in patients with atrial fibrillation (AF) undergoing percutaneous coronary intervention (PCI) (1-4).

 As regards safety, which was the primary end-point in all studies and for which most studies have been powered, a consistent reduction of major and/or clinically significant bleeding with NOAC-based double therapy as compared to warfarin-based triple therapy was observed (1-4). By pooling and meta-analyzing the safety results of the 4 studies with NOAC in AF patients undergoing PCI, a significant overall decrease by 34% in major bleeding or clinically relevant non-major bleeding was reported (risk ratio [RR] 0.66; 95% confidence intervals [CI] 0.56-0.78; p=0.0001) (5). Hence, current recommendations for early initiation or to prefer double therapy, especially using a NOAC as the oral anticoagulant, over triple therapy using warfarin as the oral anticoagulant (6) (Figure 1A), are further clear.

 As regards efficacy, no significant differences in the occurrence of the composite of death, myocardial infarction, stent thrombosis, and stroke/systemic embolism, was found in any of the 4 studies between a NOAC-based double therapy as compared to the warfarin-based triple antithrombotic regimen (1-4). However, none of the studies was adequately powered to detect differences in the rarer efficacy outcomes, and especially in myocardial infarction and stent thrombosis (1-4). By pooling and meta-analyzing the main efficacy outcomes of the 4 studies with NOAC in AF patients undergoing PCI, the absence of overall efficacy differences between NOAC-based double therapy as compared to warfarin-based triple therapy was confirmed (RR 1.08; 95% CI 0.95-1.23) (5). When focusing on the individual components of the main efficacy outcomes, again no difference was observed in the overall occurrence of stroke (RR 1.00; 95% CI 0.69-1.45) (5), while a non significant trend towards an increased rate of myocardial infarction (RR 1.22; 95% CI 0.99-1.52), as well as of all-cause death (RR 1.10; 95% CI 0.91-1.34) and cardiovascular death (RR 1.10; 95% CI 0.86-1.41), and a significant increase of stent thrombosis (RR 1.59; 95% CI 1.01-2.50) were reported (5). A signal of a potentially higher risk of myocardial ischemic events with double therapy was previously observed in both RE-DUAL PCI (3) and AUGUSTUS (4) trials, with dabigatran 110 mg and apixaban, respectively,. This finding was confirmed in the ENTRUST-AF PCI study (1), where the increase in myocardial ischemic events was seen early after cessation of aspirin in the warfarin-based triple therapy arm, as it was the case for the higher incidence of stent thrombosis in the AUGUSTUS trial (7). Thus, an initial period of triple therapy may be warranted in all patients with AF undergoing PCI. The minimum duration of such initial triple therapy course remains to be determined, but is likely in the range of 1-4 weeks. In accordance, an updated algorithm for the management antithrombotic therapy in AF patients undergoing PCI should advisably take into account these considerations, as depicted in Figure 1B.

REFERENCES

1. 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 Sep 2. pii: S0140-6736(19)31872-0.
2. 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 KAl. 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, 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 Investigator. 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, 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.; AUGUSTUS Investigators. Antithrombotic Therapy after Acute Coronary Syndrome or PCI in Atrial Fibrillation. N Engl J Med 2019;380: 1509-24.
5. Gargiulo G, Goette A, Tijssen J, Eckardt L, Lewalter T, Vranckx P, Valgimigli M.Safety and efficacy outcomes of double vs. triple antithrombotic therapy in patients with atrial fibrillation following percutaneous coronary intervention: a systematic review and meta-analysis of non-vitamin K antagonist oral anticoagulant-based randomized clinical trials. Eur Heart J 2019 Oct 25. pii: ehz732. doi: 10.1093/eurheartj/ehz732.
6. Lip GYH, Collet JP, Haude M, Byrne R, Chung EH, Fauchier L, Halvorsen S, Lau D, Lopez-Cabanillas N, Lettino M, Marin F, Obel I, Rubboli A, Storey RF, Valgimigli M, Huber K; ESC Scientific Document Group. 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 1;21: 192-3.
7. 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 2019 Nov 11. doi: 10.1161/CIRCULATIONAHA.119.044584.

LEGEND OF FIGURE

Figure 1: Algorithm for the management of antithrombotic therapy in AF patients undergoing PCI: current version (A) (5) and updated proposal based on efficacy considerations (B). AF: atrial fibrillation; PCI: percutaneous coronary intervention; O: oral anticoagulant; A: aspirin; C; clopidogrel; mo.: months;