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

AN UPDATED PROPOSAL BASED ON EFFICACY CONSIDERATIONS.

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*Short title*

ANTITHROMBOTIC THERAPY IN AF PATIENTS UNDERGOING PCI: AN UPDATED PROPOSAL

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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.

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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;