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Double Jeopardy: Will the new trials tell us how to manage patients with atrial fibrillation and coronary artery disease?

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Atrial fibrillation (AF) is a common arrhythmia disorder associated with increased morbidity and mortality, primarily driven by myocardial ischemia, heart failure and stroke. Present therapy with antiarrhythmic drugs is still unsatisfactory and stroke prevention with anticoagulants require careful consideration of concomitant bleeding risks [1,2]. Patients afflicted with AF are burdened with a vastly increased risk of thromboembolism and ischemic stroke, particularly those with coronary artery disease (CAD). The complex relationship between AF and thrombotic risk remains poorly understood. A state of AF can drive a procoagulant platelet phenotype, but aberrant platelet activation is not consistently observed in patients with AF; moreover, the IMPACT trial demonstrated there is no clear temporal association between AF and stroke [3]. The best management of patients with AF and CAD is therefore a matter of controversy and a weighing-up of individual risks and benefits.

Current guidelines recommend a triple therapy (TT) approach for patients with AF who present with CAD and acute coronary syndrome (ACS) requiring percutaneous coronary intervention PCI [4]. The downsides of combining oral anticoagulation with dual antiplatelet therapy are total annual bleeding rates of up to 44% and annual mortality of up to 6% [5,6]. With an estimated prevalence of AF of 1–2%, and ~20% of these patients requiring PCI over time [4,7], between 1 and 2 million patients in Europe will present with the combined risks of thrombosis on the one hand, and excessive bleeding on the other. The guidelines clearly recommend TT immediately after PCI for a specified period of time, but for this high-risk patient group, is prolonged TT truly best-practice?

Several registry studies have suggested that oral anticoagulation with clopidogrel is superior in terms of safety and efficacy in patients with AF and CAD [8,9], however almost no controlled randomized trials addressed the topic specifically until the WOEST trial published in 2013 [5]. As the first study to test a dual antithrombotic approach by omitting acetylsalicylic acid from the traditional TT regimen, WOEST provided evidence for improved bleeding risk with a vitamin-K-antagonist (VKA) plus clopidogrel, as well as increased efficacy. However, the trial had several important limitations, including small sample number and no pre-specified inclusions of ACS. New trials have been initiated since the introduction of the direct oral anticoagulants (DOAC), many of which are still ongoing. Table 1 summarizes the key characteristics of the major completed and continuing clinical trials on treatment strategies in patients with an indication for oral anticoagulation. Among these, WOEST [5], PIONEER AF-PCI [10], RE-DUAL PCI [11], AUGUSTUS [12], MANJUSRI [13] and APPROACH-ACS-AF (https://clinicaltrials.gov/ct2/show/NCT02789917) compare standard TT to dual therapy, with intention to reduce bleeding events. The PIONEER AF-PCI, RE-DUAL PCI and AUGUSTUS trials have been completed, and published results show that a dual regimen including a DOAC and one P2Y12-inhibitor reduce bleeding without compromising antithrombotic efficacy. Important to note here: none of Pioneer, Re-DUAL or Augustus actually have sufficient power to demonstrate efficacy on isolated ischemic events. The ISAR-TRIPLE trial merely compared a distinct duration of TT and failed to show a significant difference with respect to the clinical endpoint including bleeding events [6].

It is noteworthy that not one of the trials addresses efficacy endpoints with sufficient statistical power. AUGUSTUS was the first trial that allowed a clear head-to-head comparison of DOAC vs. VKA and could show significantly lower bleeding rates among patients with an intake of apixaban compared to VKA, as well as reduced rates of rehospitalizations, without a rise of ischemic events [12]. Evidence for DOACs in the context of TT in getting stronger, but open questions concerning elderly patients or patients with renal insufficiency will have to be answered.

We await with interest the verdict on which approach is the most promising treatment choice for AF patients undergoing PCI for treatment of CAD in the future, while the guidelines keep on evolving [14].

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Table 1
Major ongoing clinical trials on treatment strategies in patients with indication for OAC undergoing PCI.

Trial	Study cohort	No. of patients	Treatment	Duration of triple therapy	Design	Strategy	Primary endpoint
APPROACH-ACS-AF https://clinicaltrials.gov/ct2/show/NCT02789917 (NCT02789917)	PCI patients (only ACS) with indication for OAC (100% AF)	400	VKA + ASA + Clopidogrel vs. Apixaban (full dose) + Clopidogrel	1 to 6 months according to bleeding risk	Randomized, multicenter, prospective	Dual (with DOAC) vs. triple therapy	BARC ≥2 bleeding during 6 months of FU
WOEST [5] (NCT02164864)	PCI patients (all comers) and indication for OAC (69% AF)	573	Warfarin + Clopidogrel + ASA vs. Warfarin + Clopidogrel	At least 1 month in BMS (32% of patients), 12 months in DES (65%)	Randomized, multicenter, prospective	Dual vs. triple therapy	Combined end-point of minor, moderate or major bleeding complications during the initial hospitalization & 1 year of FU (TIMI & GUSTO criteria).
ISAR-TRIPLE [6] (NCT00776633)	PCI patients (all comers) and indication for OAC (100% AF)	614	VKA + ASA + Clopidogrel	6 weeks vs. 6 months	Randomized, multicenter, prospective	Triple therapy for different duration	Composite of death, myocardial infarction, definite stent thrombosis, stroke or major bleeding (in 9 months of FU)
PIONEER -AF-PC [10] (NCT01830543)	PCI patients (all comers) and indication for OAC (100% AF)	2124	Rivaroxaban 15 mg + Clopidogrel/ Prasugrel/ Ticagrelor vs. Rivaroxaban 2,5 mg + ASA + Clopidogrel/ Prasugrel/ Ticagrelor vs. VKA + ASA + Clopidogrel/ Prasugrel/ Ticagrelor	1 (16% of patients) 6 (35%), 12 months (49%) according to randomization	Randomized, multicenter, prospective	Dual (with DOAC) vs. triple therapy in two different strategies (low dose DOAC vs. VKA)	Number of participants with clinically significant bleeding (12 months of FU), defined as a composite of TIMI major and minor bleeding, and bleeding requiring medical attention.
AUGUSTUS [12] (NCT02415400)	PCI patients (all comers) and indication for OAC (100% AF)	4600	Apixaban + Clopidogrel vs. VKA + Clopidorel AND ASA vs. placebo	6 months	Randomized, multicenter, prospective	Dual therapy vs. triple therapy AND Apixaban vs. Warfarin	ISTH Major bleeding or clinically relevant non-major bleeding (in 6 months of FU)
RE-DUAL- PCI [11] (NCT02164864)	PCI patients (all comers) and indication for OAC (100% AF)	2800	Dabigatran 110 mg/150 mg + Clopidogrel/ Ticagrelor Vs. Warfarin + Clopidogrel/Ticagrelor + ASA	1 month BMS (15% of patients), 3 months DES (83%)	Randomized, multicenter, prospective	Dual (with DOAC) vs. triple therapy	Time to first TIMI Major Bleeding Event or Clinically Relevant Non Major Bleeding Event
ENTRUST-AF-PCI (NCT02866175)	PCI patients (all comers) and indication for OAC (100% AF)	1500	Edoxaban + Clopidogrel/ Prasugrel/ Ticagrelor Vs. Marcumar + Clopidogrel/ Prasugrel/ Ticagrelor + ASA	1–12 months	Randomized, multicenter, prospective	Comparison of two dual therapy regimes (Edoxaban vs. Marcumar)	Number of Major or Clinically Relevant non-major ISTH-defined Bleeding (MCRB) (in 12 months of FU)
MANJUSRI [13] (NCT02206815)	PCI patients (all comers) and indication for OAC (100% AF)	296	Ticagrelor + Warfarin Vs. Clopidogrel + ASA + Warfarin	6 months	Randomized, multicenter, prospective	Dual vs. triple therapy	Overall bleeding events (in 6 months of FU)

ACS = acute coronary syndrome, AE = adverse event, AF = atrial fibrillation/flutter, ASA = acetysalicylic acid, BARC = bleeding academic research consortium, FU = follow-up, GUSTO = Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries, MACCE = major adverse cardiac and cerebrovascular events, DOAC = new oral anticoagulation, OAC = oral anticoagulation, PCI = percutaneous coronary intervention, TIMI = Thrombolysis in Myocardial Infarction. VKA = vitamin K antagonist.

Declarations of interest

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