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 \cite{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 \cite{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 \cite{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\% \cite{5,6}. With an estimated prevalence of AF of 1–2\%, and \textasciitilde20\% of these patients requiring PCI over time \cite{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 \cite{8,9}, however almost no controlled randomized trials addressed the topic specifically until the WOEST trial published in 2013 \cite{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 \cite{5}, PIONEER AF-PCI \cite{10}, RE-DUAL PCI \cite{11}, AUGUSTUS \cite{12}, MANJUSRI \cite{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 published, 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 \cite{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 \cite{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 \cite{14}. 

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\begin{table}[h]
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\hline
\textbf{Trial}       & \textbf{Design} \rule{0pt}{2ex} \\
\hline
WOEST \cite{5}      & WOEST was the first trial to compare two different treatments for patients with AF and CAD, with a head-to-head comparison of DOAC vs. VKA \rule{0pt}{2ex} \\
\hline
PIONEER AF-PCI \cite{10} & PIONEER AF-PCI was the first trial to compare a dual antithrombotic approach with a traditional TT regimen, using a DOAC and one P2Y12-inhibitor \rule{0pt}{2ex} \\
\hline
RE-DUAL PCI \cite{11} & RE-DUAL PCI was the first trial to compare a dual antithrombotic approach with a traditional TT regimen, using a DOAC and one P2Y12-inhibitor \rule{0pt}{2ex} \\
\hline
AUGUSTUS \cite{12}  & AUGUSTUS was the first trial to compare a dual antithrombotic approach with a traditional TT regimen, using a DOAC and one P2Y12-inhibitor \rule{0pt}{2ex} \\
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MANJUSRI \cite{13}  & MANJUSRI was the first trial to compare a dual antithrombotic approach with a traditional TT regimen, using a DOAC and one P2Y12-inhibitor \rule{0pt}{2ex} \\
\hline
APPROACH-ACS-AF (https://clinicaltrials.gov/ct2/show/NCT02789917) & APPROACH-ACS-AF was the first trial to compare a dual antithrombotic approach with a traditional TT regimen, using a DOAC and one P2Y12-inhibitor \rule{0pt}{2ex} \\
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Declarations of interest

Reza Wakili: consultant/speaker fees from Boehringer Ingelheim, Daiichi Sankyo, Bayer and Pfizer.

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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         | PCI patients (only ACS) with indication for OAC (100% AF) | 400             | VKA + ASA + Clopidogrel vs. Apixaban (full dose) + Ticagrelor               | 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    |
| AUGUSTUS [12]          | PCI patients (all comers) and indication for OAC (100% AF) | 2124            | Rivaroxaban 15 mg + Clopidogrel vs. Prasugrel/Ticagrelor                    | (6 (16% of patients) 6 (35%), 12 months (49%) according to randomization) | Randomized, multicenter, prospective           | Dual (with DOAC) vs. triple therapy         | ISTH Major bleeding or clinically relevant non-major bleeding (in 6 months of FU) |
| RE-DUAL-PCI [11]       | PCI patients (all comers) and indication for OAC (100% AF) | 2800            | Dabigatran 110 mg/150 mg + Clopidogrel/Ticagrelor vs. Warfarin + Clopidogrel/Ticagrelor | 1 month BMS (5% of patients), 3 months DES (83%) | Randomized, multicenter, prospective           | Dual therapy vs. triple therapy AND Apixaban vs. Warfarin | Time to first TIMI Major Bleeding Event or Clinically Relevant Non Major Bleeding Event |
| ENTRUST-AF-PCI          | PCI patients (all comers) and indication for OAC (100% AF) | 1500            | Edoxaban + Clopidogrel vs. Prasugrel/Ticagrelor vs. Marcumar + Clopidogrel/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 (MCBR) (in 12 months of FU) |
| MANJUSRI [13]          | PCI patients (all comers) and indication for OAC (100% AF) | 296             | Ticagrelor vs. Warfarin + Clopidogrel/Ticagrelor + ASA vs. 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 = acetylsalicylic 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.
interventions: a joint consensus document of the European Society of Cardiology Working Group on Thrombosis, European Heart Rhythm Association (EHRA), European Association of Percutaneous Cardiovascular Interventions (EAPCI) and European Association of Acute Cardiac Care (ACCA) endorsed by the Heart Rhythm Society (HRS) and Asia-Pacific Heart Rhythm Society (APHRS), Eur. Heart J. 35 (2014) 3155–3179, https://doi.org/10.1093/eurheartj/ehu298.

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