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Antithrombotic therapy in patients with atrial fibrillation undergoing PCI remains a moving target, yet with a clearer direction!

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Approximately, one out of five patients with atrial fibrillation (AF) will undergo percutaneous coronary intervention (PCI) or suffer from an acute coronary syndrome (ACS). Considering their concomitant need for sustained oral anticoagulation therapy (OAC), the challenge is to identify the optimal antithrombotic strategy to prevent thrombotic recurrences for these patients.

During the past few years, randomised clinical trials (WOEST, PIONEER AF-PCI, RE-DUAL PCI, AUGUSTUS, and ENTRUST AF-PCI) have focused on the antithrombotic treatment of patients with AF within the first 12 months after PCI[1-5]. In accordance with their findings, both European and North American guidelines recommend triple antithrombotic therapy (TAT), an oral anticoagulant plus aspirin and clopidogrel, for as short a duration as possible, mainly limited to the peri-PCI period (i.e., up to 1 week post-PCI), after which aspirin should be discontinued[6,7]. However, guideline and consensus recommendations also allow for variations in such a regimen, in terms of dual antiplatelet therapy (DAPT) duration (up to 1 month) and choice (ticagrelor or prasugrel instead of clopidogrel after aspirin discontinuation), which should be guided by a balanced, individual, assessment of competing risks: thrombosis and bleeding[7,8]. Against this background, it would be desirable for practitioners to personalise the duration of DAPT based on a prediction rule that easily identifies patients at high bleeding risk and separates patients who may potentially benefit from an abbreviated (e.g., high bleeding and low ischaemic risks) or prolonged DAPT (e.g., low bleeding risk and high ischaemic risk) duration.

In this issue of EuroIntervention, Zwart and colleagues introduce a novel risk score to identify the need for triple antithrombotic therapy, derived from the RE-DUAL PCI trial (Randomised Evaluation of Dual Antithrombotic Therapy with Dabigatran versus Triple Therapy with Warfarin in Patients with Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention), and externally validated in a simultaneously published cohort (n=1,059 patients) from the WOEST 2 registry (ClinicalTrials.gov: NCT02635230)[9]. This 6-item risk score allowed the identification of a small patient cohort (n=154, 5.7%) with a score ≥5 with predicted high(er) thrombotic risk, in whom a significant reduction of myocardial infarction (MI) or stent thrombosis (ST) was observed with TAT vs DAT (6.3% vs 21.0%, p=0.04), without bleeding liability. The risk score showed a modest to fair discrimination of the composite ischaemic endpoint in both the derivation and validation cohorts at a concordance (c-) statistic value of 0.66 (95% confidence interval [CI]: 0.62-0.69) and 0.63 (95% CI: 0.56-0.70) respectively. Some points lower than the multivariable Cox regression model but higher than for the CHA_2DS_2-VASc in the RE-DUAL PCI cohort: 0.58 (95% CI: 0.54-0.62).

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The authors should be greatly commended for having addressed an important research question and a major, so far unmet, clinical need. This is the first study exploring the role of baseline ischaemic risk factors modelled into a simple score for the decision-making on DAPT duration for AF patients after PCI. However, it

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may be argued that the findings from this *post hoc* analysis cannot be conclusive considering several limitations, as outlined below.

In the RE-DUAL PCI trial, the duration of DAPT was limited to the vitamin K antagonist (VKA)-treated patients (n=939 patients) and guided by the type of stent used: TAT was limited to one month in VKA patients treated with bare metal stents (n=113) and three months in patients (n=826) if a drug-eluting stent was used. So, TAT with VKA was compared to DAT with a NOAC, which may have exaggerated the bleeding risk in the former group.

Also, patients with a score ≥5 contributed only a small minority of ischaemic events in the first year following randomisation (31/209, 14.83%) in the RE-DUAL PCI trial. One cannot rule out that the results of this analysis are just reflecting a play of chance. The c-statistic of 0.63 in the validation cohort, as acknowledged by the authors, only applies to the overall fit of the risk score and does not necessarily correspond to the ability of the score to identify patients at higher risk of events if more prolonged TAT is not given.

Moreover, the RE-DUAL PCI trial was not powered to explore the treatment effect with respect to ischaemic endpoints in the overall population nor to explore any safety or efficacy endpoint in subgroups. The number of stent thromboses was low overall. The use of potent $P2Y_{12}$-inhibitors such as ticagrelor in combination with oral anticoagulation was limited to a small subset of patients and not randomised.

Finally, the recently published MASTER-DAPT (The Management of High Bleeding Risk Patients Post Bioresorbable Polymer Coated Stent Implantation With an Abbreviated Versus Standard DAPT Regimen) trial demonstrated that one month of dual antiplatelet therapy was non-inferior to treatment continuation for at least 2 additional months for the occurrence major adverse clinical events and reduced major or clinically relevant non-major bleeding[8]. This was unlike at least some of the previous trials, including RE-DUAL PCI, which showed an early trade-off between ischaemic and bleeding risks with shorter than 1-month DAPT[2,3,5]. One-month DAPT in OAC patients in the MASTER DAPT trial was not associated with great MI or ST risks[10]. Therefore, longer than 1-month DAPT in OAC patients is probably an outdated treatment duration. Whether this new risk score properly identifies patients who would benefit from 1-month as opposed to ~1-week DAPT remains to be investigated.

In conclusion, further validation and eventually refinements of this (or alternative) risk score(s) in larger populations of patients with AF-PCI are warranted. Yet, glory to the RE-DUAL PCI investigators who continue moving the field in search of the best treatment for each individual patient[9].

Conflict of interest statement

P. Vranckx reports consulting fees from Daiichi Sankyo and personal fees from Daiichi Sankyo, Bayer AG, CSL Behring, and Novartis, is Editor in Chief of EJH ACVC and is on the ESC Publications Committee. M. Valgimigli reports grants and personal fees from Terumo; and personal fees from AstraZeneca, Alvimedica/CID, Abbott Vascular, Daiichi Sankyo, Bayer, CoreFlow, Idorsia Pharmaceuticals LTD, Universität Basel, Dept Klinische Forschung, Vifor, Bristol Myers Squib SA, Biotronik, Boston Scientific, Medtronic, Vesalio, Novartis, Chiesi, and PhaseBio.

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