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Twelve-Month Outcome of Patients with an Established Indication for Oral Anticoagulation Undergoing Coronary Artery Stenting and Stratified by the Baseline Risk of Bleeding☆ Insights from the *War*farin and Coronary *Stent*ing (War-Stent) Registry

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ABSTRACT

Purpose: To evaluate the outcome of patients with an established indication for oral anticoagulation (OAC) undergoing coronary stent implantation (PCI-S) and stratified by the baseline risk of bleeding.
Material and methods: The database of the prospective, multicentre, observational WAR-STENT registry (ClinicalTrials.gov identifier NCT00722319) was analyzed and patients with atrial fibrillation and CHA_2DS_2-VASc score ≥2, mechanical heart valve, prior cardiac embolism, intra-cardiac thrombus and recent venous thromboembolism who were treated with either triple (warfarin, aspirin and clopidogrel) or dual (warfarin and clopidogrel) or dual antiplatelet (aspirin and clopidogrel) therapy, identified. Patients were then sorted into two groups at non-low and low risk of bleeding, as defined by an ATRIA score >3 and ≤3 respectively, and compared regarding major adverse cardiac and vascular events (MACVE) and bleeding.
Results: At 12-month follow up, MACVE were comparable in the two groups, whereas total, major and minor bleeding, as well as combined MACVE and total bleeding, were significantly more frequent in the non-low bleeding risk group. Upon Cox univariate and multivariable analysis, non-low bleeding risk category confirmed as an independent predictor of major bleeding. The choice of antithrombotic therapy however, appeared not to be influenced by the bleeding risk category at baseline.
Conclusions: In patients with an established indication for OAC undergoing PCI-S, non-low bleeding risk category is the most potent independent predictor of major bleeding. Stratification of the bleeding risk at baseline should therefore be regarded as an indispensable process to be carried out before selection of the antithrombotic therapy.

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1. Introduction

In patients on oral anticoagulation (OAC) with warfarin undergoing percutaneous coronary intervention with stent (PCI-S), the optimal antithrombotic therapy remains largely undefined. Whereas triple therapy (TT) of warfarin, aspirin and clopidogrel is generally recommended [1], the evidence in support of this regimen is not univocal [2]. Recent clinical studies, observational registries and meta-analyses suggest that alternative antithrombotic regimens, namely dual therapy (DT) of warfarin and the single antiplatelet agent clopidogrel or even dual antiplatelet therapy (DAPT) of aspirin and clopidogrel, may be comparably effective and safe to TT [3–9]. Also, DT of the non-vitamin K-antagonist oral anticoagulant (NOAC) rivaroxaban and clopidogrel has recently emerged as a possible alternative to conventional TT [10].

Apart from the variable study design and populations enrolled, the discordance in observations may be related to the common inclusion of patients with no or weak indication for OAC, such as, those with atrial fibrillation and CHA_2DS2_2-VASc score <2 or with remote venous thromboembolism, in whom the benefit of combined antithrombotic therapy on thromboembolic events may be easily outweighed by the increased risk of bleeding carried by combined anticoagulant and antiplatelet therapy. Risk of bleeding which in turn, may largely be different depending on the baseline patient characteristics.

To evaluate the antithrombotic management and outcome of patients with an established indication for OAC undergoing PCI-S and stratified by the baseline risk of bleeding, the database of the prospective, multicenter WARfarin and coronary STENTing (WAR-STENT) registry was analyzed.

2. Material and methods

The WAR-STENT registry is a prospective, multicentre, observational study including consecutive patients on OAC with warfarin who underwent PCI-S at 37 Italian centers between November 2008 and June 2010 (ClinicalTrials.gov identifier NCT00722319). Ongoing warfarin at the time of PCI-S or when PCI-S was planned was the only inclusion criterion. Owing to the observational design, no exclusion criteria were provided, except for the patient's refusal to participate. At each center, patients were treated according to local policies, and were followed for 12 months. Local ethic committees approved the study protocol, and written informed consent was obtained from every patient.

The outcome measures considered for this work were the incidence at 12-month follow up of: (1) major adverse cardiac and vascular events (MACVE), including cardiovascular death, non-fatal myocardial infarction (MI), target vessel revascularization, stent thrombosis, stroke, and venous thromboembolism (VTE); (2) major, minor and total bleeding, and 3) combination of both MACVE and total bleeding.

Outcome definitions were: (1) cardiovascular death: related to cardiac causes or thromboembolism; (2) MI: according to the third universal definition [11]; (3) target vessel revascularization: any re-intervention (percutaneous or surgical) to treat a stenosis in the same coronary vessel treated at the index procedure, within and beyond the target lesion limits; (4) stent thrombosis: according to Academic Research Consortium classification [12]; (5) stroke: permanent focal neurological deficit adjudicated by a neurologist, and confirmed by neuroimaging; (6) VTE: signs/symptoms of deep vein thrombosis/pulmonary embolism associated with a positive imaging test; and (7) major and minor bleeding: according to TIMI classification [13].

Patients with an established indication for OAC, defined as those with atrial fibrillation and CHA_2DS_2-VASc score ≥2, mechanical heart valve, prior cardiac embolism, intra-cardiac thrombus and recent (i.e., <6 months) VTE, who were discharged alive after PCI-S on either TT, DT or DAPT, were identified. After stratification in two groups at non-low and respectively low risk of bleeding, namely with ATRIA score >3 and respectively ≤3 [14], patients were then compared as regards the antithrombotic therapy and incidence of MACVE, bleeding complications and combination of both at 12 months.

2.1. Statistical analysis

Continuous variables were expressed as mean ± standard deviation. Categorical variables were expressed as percentages. Student *t*test or Wilcoxon rank-sum test were used as appropriate for comparison of continuous data. Chi-square test was used for comparison of categorical variables. The effect of baseline bleeding risk category on different outcomes (i.e., MACVE, major bleeding, total bleeding, and MACVE plus total bleeding) was estimated with Kaplan–Meier method, and differences between groups were assessed with log-rank test. The contribution of clinical variables to the composite outcome of MACVE and major bleeding was identified by Cox univariate analysis. Multivariable Cox proportional hazard analysis was then performed by entering into the model variables with a p-value <0.1 on univariate analysis. The proportional hazards assumption was tested by using the Schoenfeld residuals. The goodness of fit of multivariable Cox regression models was evaluated by the Harrell's C statistic. A p value <0.05 was considered statistically significant. Analyses were performed using Stata/SE 12.1 statistical software (StataCorp LP, College Station, TX, USA).

3. Results

Out of the overall 373 patients with an established indication for OAC included in the WAR-STENT registry who were treated with either TT, DT or DAPT, 46 (12%) were classified at non-low bleeding risk (i.e., ATRIA score >3) (Table 1). Compared to patients at low bleeding risk, patients at non-low bleeding risk were significantly older and had a significantly higher prevalence of previous coronary revascularization, previous bleeding, renal failure and anemia (Table 1). In accordance, the ATRIA score was significantly higher in patients at non-low bleeding risk (Table 1). Neither regarding the remaining clinical variables nor the indication for both OAC and PCI-S, further significant differences between groups were observed (Table 1).

At discharge, the prescription rate of TT, DT and DAPT was comparable in the two groups (Table 2). Also comparable were the median durations of clopidogrel prescription and the proportion of the different ranges of International Normalized Ratio (INR) recommended at discharge in patients on TT (Table 2).

At 12-month follow up, the incidence of total MACVE was comparable in the two groups (Table 3). Also comparable was the incidence of the individual MACVE (Table 3). Total, major and minor bleeding events were significantly more frequent in the non-low bleeding risk group, as it also was the incidence of combined MACVE plus total bleeding (Table 3). In patients at non-low bleeding risk, the relative risk of major bleeding was significantly higher (odds ratio [OR] 4.37; 95% confidence intervals [CI] 1.74–11.00; $p = 0.001$).

No significant difference between the two groups was observed regarding the sites at which major bleeding events occurred (Table 4). The sites of minor bleeding events were also comparable, with the exception of nose bleeds which were more frequent in the non-low risk group (Table 4). Irrespective of the bleeding risk category, no significant difference was observed in the antithrombotic treatment ongoing at the time of either major or minor bleeding (Table 4).

The event-free survival at 12 months, as estimated by Kaplan–Meier curves, was comparable in the two groups regarding MACVE, whereas it was significantly lower in the non-low bleeding risk group regarding major and total bleeding, as well as combined MACVE and total bleeding (Fig. 1A-D).

Upon both Cox univariate and multivariable analyses, concomitant aspirin treatment was identified as the only independent predictor of (significantly lower incidence) of MACVE (OR 0.37, 95% CI 0.18–0.72; $p = 0.02$, and 0.35, 95% CI 0.16–0.75; $p = 0.007$, respectively). Age, congestive heart failure, renal failure, anemia, ATRIA score and non-low bleeding risk category were independent predictors of (significantly higher incidence) of major bleeding at Cox univariate analysis

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