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Impact of percutaneous coronary intervention extent, complexity and platelet reactivity on outcomes after drug-eluting stent implantation

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ABSTRACT

Background: Risk stratification after percutaneous coronary intervention (PCI) is mainly based on demographics and clinical presentation (stable coronary artery disease [CAD] vs. acute coronary syndromes [ACS]). We investigated the impact of PCI extent and complexity on 2-year clinical outcomes after successful implantation of drug-eluting stents (DES) and whether this effect is influenced by clinical presentation and/or high platelet reactivity (HPR) on clopidogrel.

Methods and results: Patients from the prospective, multicenter Assessment of Dual Antiplatelet Therapy with Drug-Eluting Stents study were stratified according to PCI complexity, with complex PCI (C-PCI) defined as ≥3 stents implanted, bifurcation PCI with 2 stents, rotational atherectomy use for severely calcified lesions, or left main or saphenous vein graft (SVG) PCI. Major adverse cardiac events (MACE; cardiac death, myocardial infarction, and stent thrombosis) were compared at 2-year follow-up in patients with and without C-PCI. Successful DES PCI was performed in 8582 patients—2255 (26.3%) with C-PCI. C-PCI was independently associated with higher 2-year risk of MACE (adjusted HR [adjHR]: 1.56; 95%CI: 1.29–1.89; $p < 0.0001$), MI (adjHR: 1.71; 95%CI: 1.37–2.14; $p < 0.0001$), and ST (adjHR: 2.26; 95%CI: 1.42–3.59; $p = 0.0006$). The association between C-PCI vs. non–C-PCI and the risk of MI and ST was greater in stable CAD than in ACS ($P_{interaction} = 0.04$ and 0.03, respectively). SVG PCI, 2-stent bifurcation treatment, and implantation of ≥3 stents were independently associated with MACE.

Conclusions: Patients undergoing extensive and more complex PCI experienced worse outcomes after successful PCI. Considering the extent and complexity of PCI revascularization may improve risk stratification.

1. Introduction

Risk stratification after percutaneous coronary intervention (PCI) is mainly based on demographic characteristics (e.g. age, diabetes) and clinical presentation (stable coronary artery disease [CAD] vs. acute coronary syndrome [ACS]), and if available, platelet reactivity testing [1–6]. The duration and intensity of post-PCI dual antiplatelet therapy (DAPT) are also largely conditioned by the presence or absence of these risk factors [7–10]. Whether the complexity and the extent of CAD, and consequently the complexity of PCI performed, independently influences the long-term occurrence of adverse events after successful PCI in the drug-eluting stent (DES) era remains undetermined. We therefore sought to investigate the impact of PCI complexity on the occurrence of adverse events after successful DES implantation, and to determine whether this association is influenced by clinical presentation and/or platelet reactivity on clopidogrel from the large-scale Assessment of Dual Antiplatelet Therapy With Drug-Eluting Stents (ADAPT-DES) study [11].

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2. Methods

2.1. Study population

ADAPT-DES was a prospective, multicenter, observational study specifically designed to determine the association between platelet reactivity on clopidogrel and stent thrombosis (ST) after successful DES implantation. The design and primary results of ADAPT-DES have been previously reported [11]. Briefly, a total of 8582 "all-comer" patients were prospectively enrolled at 11 sites in the US and Germany. All patients who were successfully treated with one or more DES were eligible for enrollment, regardless of clinical presentation or procedural complexity. The only major exclusion criteria were intra- or periprocedural major complications, or planned bypass surgery after PCI. Platelet reactivity on aspirin and clopidogrel were assessed after an adequate loading period to ensure full antiplatelet effect using the VerifyNow Aspirin, P2Y12, and IIb/IIIa assays (Accumetrics, San Diego, CA, USA). After PCI, patients were treated with aspirin indefinitely, and clopidogrel was recommended for at least 1 year. All other treatments were as per standard of care. Clinical follow-up was scheduled at 30 days, 1 year, and 2 years. An independent clinical events committee adjudicated ischemic events using original source documents. The institutional review board at each participating center approved the study, and all eligible patients signed written informed consent prior to enrollment.

In the present study, outcomes in patients included in the ADAPT-DES study were examined according to procedural complexity. Subsequently, we further stratified the study population according to the clinical presentation (stable CAD or ACS [non-ST-segment elevation or ST-segment elevation myocardial infarction) and the presence of high platelet reactivity (HPR) on-clopidogrel.

2.2. Study objectives and definitions

Our objectives were to: (i) determine the impact of PCI complexity on the occurrence of adverse ischemic events occurring within 2 years after successful DES implantation; (ii) assess the influence of clinical presentation and HPR on the association between PCI complexity and clinical outcomes; and (iii) characterize the combined effects of PCI complexity, clinical presentation, and HPR on the subsequent risk of adverse ischemic events.

We defined complex PCI (C-PCI) as an elective or urgent PCI with any of the following characteristics: ≥3 DES implanted, bifurcation PCI with 2 stents, left main (LM) coronary artery PCI, saphenous vein graft (SVG) PCI, and rotational atherectomy use for a severely calcified lesion. HPR on clopidogrel was defined as >208 platelet reactivity units (PRU). Major adverse cardiac events (MACE) were defined as the composite of cardiac death, MI, or stent thrombosis (ST) [11]. Other endpoints evaluated in the present study included all-cause mortality, cardiac mortality, target vessel failure (TVF), ischemia-driven target lesion revascularization (TLR) and ischemia-driven target vessel revascularization (TVR), and major bleeding. MI was defined according to the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) criteria [11,12]. Definite or probable ST was defined according to the Academic Research Consortium definition [13]. TVF was defined as the composite of all-cause death, MI, or ischemia-driven TVR. Major bleeding was defined as the occurrence of any of the following: A Thrombolysis In Myocardial Infarction (TIMI) major or minor bleed, a Global Use of Strategies to Open Occluded Arteries (GUSTO) severe or moderate bleed, an ACUITY major bleed, or any clinically significant bleeding event requiring medical attention [11].

2.3. Statistical analysis

Continuous variables are presented as mean ± standard deviation and were compared with the *t*-test; categorical variables are reported as percentages and were tested with the χ^2 test. Event rates during follow-up were estimated by Kaplan-Meier methods. Unadjusted hazard ratios for 2-year outcomes were determined from Cox proportional hazards models. To avoid over fitting, the maximum number of covariates in the models was limited to the number of events divided by 10. The multivariable models included predictors known to impact prognosis entered as continuous variables (age, body mass index, and baseline hemoglobin), as binary variables (male sex, current smoker, peripheral arterial disease, congestive heart failure, previous PCI, previous coronary artery bypass graft [CABG], multivessel disease, HPR, ACS, left anterior descending artery as the target vessel, pre-procedural TIMI flow grade 2 or 3, thrombus, and use of intravascular ultrasound), and as rank-order variables (baseline creatinine clearance, baseline white blood cell concentration, and baseline platelet concentration). In regard to stent thrombosis, which was less common than the other outcomes, more parsimonious models were used. These models included the following covariates: age, diabetes, previous PCI, smoking, ACS, HPR, thrombus, and baseline platelet count. The following model diagnostics resulted in the inclusion of the three baseline variables as ranks rather than numeric values: (i) assessment of functional form of the included covariates by visual inspection of Martingale residuals; (ii) testing of the proportionality of hazards assumption by inspection of Schoenfeld residuals; (iii) ruling out the presence of influential outliers by plotting score residuals. The consistency of the effect of C-PCI according to the clinical presentation and HPR was evaluated with formal interaction testing. All tests were 2-sided, and *p*-values < 0.05 were considered statistically significant. Statistical analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC, USA).

3. Results

3.1. Clinical and procedural characteristics

Successful PCI with DES was performed in 8582 patients, 2255 (26.3%) of which were C-PCI. Implantation of ≥3 stents, SVG PCI, and LM PCI were the most frequent types of C-PCI performed (Supplemental Table 1). Baseline clinical characteristics are summarized in Table 1. Compared to non-C-PCI, patients who underwent C-PCI were older, more commonly male, and had a higher prevalence of cardiovascular and non-cardiovascular comorbidities. Patients who underwent C-PCI more commonly presented with stable CAD rather than ACS, and had more extensive CAD and lower ejection fraction. There were no significant differences in on-clopidogrel PRU or in the prevalence of HPR after C-PCI and non-C-PCI procedures.

Procedural characteristics are shown in Table 1. Compared to non-C-PCI, patients who underwent C-PCI were more commonly treated through a femoral rather than radial approach, had a greater number of vessels and lesions treated, had greater total stent length and more stents implanted. Intravascular ultrasound was used to a similar extent in both groups, but was more often used in the C-PCI group to guide and optimize the procedure.

Medications used during the study period in patients with and without C-PCI are summarized in Supplemental Table 2. There were no significant differences in dual antiplatelet therapy (DAPT) use through 2 years of follow-up. Patients who underwent C-PCI were more commonly treated with warfarin through the study period.

3.2. Two-year clinical outcomes according to procedural complexity

Compared to non-C-PCI, patients who underwent C-PCI had higher 2-year rates of all-cause mortality (Fig. 1A), MACE (Fig. 1B), ST (Fig. 1C), MI, ischemia-driven revascularization, and major bleeding (Table 2). Following adjustment for differences in baseline covariates, C-PCI remained associated with a higher 2-year risk of MACE (adjusted HR: 1.56; 95% CI: 1.29–1.89; $p < 0.0001$), MI (adjusted HR: 1.71; 95% CI: 1.37–2.14; $p < 0.0001$), ST (adjusted HR: 2.26; 95% CI: 1.42–3.59; $p = 0.0006$), ischemia-driven revascularization (adjusted HR: 1.90; 95% CI: 1.63–2.22; $p < 0.0001$), and major bleeding (adjusted HR: 1.31; 95% CI: 1.11–1.55; $p = 0.002$) (Table 2). The complete lists of the independent predictors in these multivariable models appear in Supplemental Tables 3 to 11). For all adverse events, no interactions were present when stratified by diabetes status and first- versus second-generation DES (Supplemental Table 12 and Supplemental Table 13).

Supplemental Fig. 1 shows Kaplan-Meier failure rates for MACE and ST stratified by each C-PCI component. At 2 years, the MACE rate (Supplemental Fig. 1A) was the highest for patients undergoing SVG PCI (18.0%), followed by bifurcation PCI involving 2 stents (10.0%), PCI with ≥3 stents implanted (7.4%), and rotational atherectomy use (7.4%). LM PCI and non–C-PCI were associated with the lowest MACE rates (6.8% and 5.3%, respectively). Bifurcation PCI was associated with the highest 2-year rate of ST (Supplemental Fig. 1B; 2.8%). Non–C-PCI and LM interventions had the lowest rates of ST. The 2-year risk of MACE increased with increasing number of C-PCI components (Supplemental Fig. 2). Following multivariable adjustment (Supplemental Table 14), SVG PCI, ≥3 stents implanted, and bifurcation PCI were associated with increased 2-year rates of MACE, while rotational atherectomy use and LM PCI were not.

Landmark analyses in the periods between 0 to 6 months and 6 months to 2 years showed different patterns of events according to the type of C-PCI performed. For SVG interventions, the hazard of MACE (Supplemental Fig. 1C) continued to accrue throughout the 2-year follow-up, whereas for bifurcation PCI and ≥ 3 stents implanted, MACE rates within but not after the first 6 months were higher with C-PCI than non–C-PCI. Six-month rates of ST were the highest with rotational atherectomy use for severely calcified lesions, followed by