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Role of stent type and of duration of dual antiplatelet therapy in patients with chronic kidney disease undergoing percutaneous coronary interventions. Is bare metal stent implantation still a justifiable choice? A post-hoc analysis of the all comer PRODIGY trial☆

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ABSTRACT

Aim: Chronic kidney disease (CKD) is a powerful predictor of major cardiovascular events and stent thrombosis (ST) in patients undergoing percutaneous coronary interventions (PCI). No randomized data are available to compare, and guide the selection of type of stent between bare metal (BMS) or drug eluting stent (DES) in this population.

Methods and results: We performed a post-hoc analysis of the PROlonging Dual antiplatelet treatment after Grading stent-induced Intimal hyperplasia studY (PRODIGY) trial, in which stable or unstable patients with coronary artery disease undergoing PCI were randomized 1:1:1:1 to receive BMS, paclitaxel- (PES), zotarolimus- (ZES-S), or everolimus- (EES) eluting stent. A total of 2003 patients were randomized, and 22 patients were excluded for missing serum creatinine leading to a final population of 1981 patients. Primary outcome was definite or probable ST. We also assessed MACE (myocardial infarction, stroke, or death), and all-cause death, as secondary outcome.

CKD, defined with estimated glomerular filtration rate <60 ml/min/1.73 m^2, was found in 373 patients (18.8%). The incidence of ST at 2 years was 5.1% in CKD and 2.1% in non-CKD patients (HR 2.57, 95% confidence interval (CI) 1.46 to 4.52, $p < 0.001$). At multivariable regression we found that patients randomized to EES or ZES-S, but not PES, had lower risk of ST at two years as compared with BMS: adjusted HR = 0.288, 95% CI [0.107–0.778, $p = 0.014$] and HR = 0.394, 95% CI [0.164–0.947, $p = 0.037$] respectively. The number of patients needed to be treated to prevent 1 ST with an EES vs BMS was 20 in CKD and 50 in patients without CKD. EES patients had the lowest incident MACE events 26.4% as compared to BMS 35.1%, ZES-S 33.0%, or PES 35.7% patients, $p = 0.551$. All-cause death was lowest in ZES-S group 10.6% as compared to BMS 18.1%, PES 25.5% and EES 14.9%, $p = 0.040$. We found no significant interaction between DAPT duration (6 vs 24 months) and stent type on primary outcome, $P_{INT} = 0.47$ for BMS, $P_{INT} = 0.57$ for PES, $P_{INT} = 0.41$ for ZES-S and $P_{INT} = 0.28$ for EES.

Conclusions: In an all-comer population of patients with stable and unstable CAD, CKD at baseline was associated with a double risk of ST and MACE. CKD patients receiving EES had less than half risk of ST 2 years after PCI as compared with BMS and PES. Our analysis suggests that 2nd generation limus-based stent should be favored over paclitaxel-based DES or BMS to reduce ST and MACE in CKD patients.

1. Introduction

Chronic kidney disease (CKD) is common in patients undergoing percutaneous coronary interventions (PCI), especially in those presenting with acute coronary syndromes [1–3], and has been consistently associated with an increased risk of ischemic events, including stent thrombosis (ST) [4]. CKD is a powerful predictor of subsequent ST with more than 6-fold increased risk [5] thus raising possible concerns of using of drug eluting stents (DES) in these patients [6]. The European Guidelines for myocardial revascularization (2010) have recommended that DES should not be preferred and used indiscriminately over bare metal stents (BMS) in patients with CKD [7] although this recommendation was reformulated in the subsequent edition.

While randomized data are lacking in this setting, observations on safety and efficacy of DES in CKD patients have not supported these

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concerns and showed similar safety [8–10] or potential reduction of major adverse cardiovascular events (MACE) of DES compared with BMS [3,11]. These data however have several limitations: i) Stent type (DES or BMS) was left at operator's preference [3,8–11], ii) first-generation DES, which are known to be more susceptible to ST, were used [3,8–11] and iii) ST was not systematically collected using the Academic Research Consortium (ARC) criteria [3,10,11].

To overcome in part these limitations we performed a post-hoc analysis of the PROlonging Dual antiplatelet treatment after Grading stent-induced Intimal hyperplasia studY (PRODIGY trial) [12,13] with the primary purpose to assess, in an all-comer population of patients with stable or unstable coronary artery disease undergoing PCI, long term outcome of patients with CKD at presentation who were randomized to receive BMS, paclitaxel-eluting stent (PES), zotarolimus-eluting stent (ZES-S) or everolimus-eluting stent (EES) at the time of PCI.

2. Methods

2.1. Study design and population

The design of the PRODIGY trial has been published [14]. PRODIGY was an open label, 2 by 4 randomized, multicenter, controlled trial, testing the hypothesis that 24 months of dual antiplatelet therapy (DAPT) with aspirin and clopidogrel could reduce the composite of all-cause death, stroke, or MI as compared with 6 months DAPT in an all-comer population undergoing PCI [12]. At day 0 patients with an indication to coronary stenting randomly underwent implantation BMS (no active late loss inhibition), Endeavor Sprint ZES-S (mild late loss inhibition), PES (moderate late loss inhibition), or Xience V EES (high late loss inhibition). At 30 days, patients within each stent group were randomly assigned to receive 6 months or up to 24 months of DAPT (80 to 160 mg aspirin orally and 75 mg clopidogrel orally). The key inclusion criterion was the presence of coronary atherosclerosis requiring PCI, thus including patients with stable coronary artery disease (CAD), non-ST-segment elevation acute coronary syndrome (NSTE-ACS), or ST-segment elevation acute coronary syndrome (STE-ACS). Key exclusion criteria were: known acetylsalicylic acid or clopidogrel allergy; major surgery within 15 days; planned surgery in the following 24 months, active bleeding or bleeding diathesis; and concomitant or foreseeable oral anticoagulant treatment. All patients received an office visit at 30 days, 6 months, and 24 months after randomization.

2.2. Definitions

CKD was defined by glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2. The modification of diet in renal disease formula was used to compute eGFR:

eGFR [ml/min/1.73 m^2] = 186 * baseline SCr [mg/dl] − 1.154 * Age [years] − 0.203 * (0.742 if Female) * (1.21 if African descent).

Our primary endpoint was the incidence of definite or probable ST based on the ARC criteria [15]. Secondary endpoints considered were: the composite of all-cause death, stroke or myocardial infarction; all-cause death; myocardial infarction; stroke; and target lesion revascularization. All endpoints were assessed at 24 months. All potential endpoints were individually adjudicated by a clinical event committee blinded to randomized treatment allocation.

2.3. Statistical analysis

Baseline categorical variables were expressed as count (percentage) and compared with the χ^2 test. Baseline continuous variables were expressed as median (interquartile range) and compared with the Wilcoxon rank sum between the groups defined by CKD (binary) and ANOVA rank sum test between the groups defined by stent type (four levels).

The hazard ratios (HR) and 95% confidence interval (CI) of the four randomized groups of patients defined by stent type on outcome were estimated by fitting a Cox proportional hazard regression model with the bare metal stent group set as reference category. The association between stent type and clinical outcome was adjusted for potential confounders and established risk factors of stent thrombosis [5]. In addition to CKD (as defined above), the following covariates were included a priori into the model for risk adjustment: age, left ventricular ejection fraction (LVEF), diabetes mellitus, ACS at presentation (vs stable angina), and total stent length. Additionally, the experimental treatments 6 vs 24 month duration of dual antiplatelet therapy and stent type were included in the model.

There were no missing observations for all the covariates except for LVEF (N = 139, 6.9%) and stent length (N = 6, 0.3%). Sensitivity analysis using case-deletion and the exclusion of the aforementioned covariates were used to address the role of missingness. Sensitivity analysis by including eGFR as a continuous variable was also performed. The proportionality assumption was checked either by visual estimation of the log-cumulative hazard versus log-time (sFigure 1) or by using Schoenfeld residuals which failed to reject the null hypothesis that event rate was affected by time ($p = 0.46$). A 2-sided probability value $p \le 0.05$ was considered significant. Data were analyzed in the R version 3.1.3 software environment [16] and "Survival" package.

3. Results

3.1. Patients

From December 2006 to December 2008, 2789 patients were screened for eligibility, 2013 were randomized to one of four different stent types [12,13]. Ten patients, who withdrawn informed consent within 30 days of visit, and 22 patients who had incomplete baseline SCr data, were excluded (Fig. 1). This led to a final population of 1981 patients. Baseline variables are outlined in Table 1; 1833 were censored at 2 years of follow-up.

Overall, 373 (18.8%) patients had CKD at baseline. Within this group of patients, baseline (Table 1) and procedural (Table 2) characteristics were fairly balanced across the four stent arms. Patients allocated to the BMS group were older 78 [71–82] years compared with the ZES-S group 72 [66–79] years, PES group 76 [70–81] years and EES 75

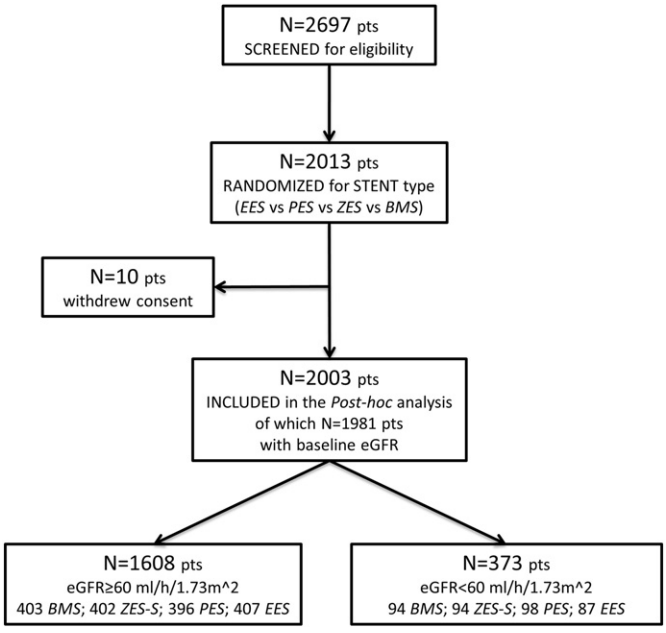

Fig. 1. Patient flow.