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Combining clinical and angiographic variables for estimating risk of target lesion revascularization after drug eluting stent placement☆

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ABSTRACT

Background: Drug-eluting stents (DES) reduce restenosis but require prolonged antiplatelet therapy, when compared with bare metal stents. Ideally, the patient should be involved in this risk:benefit assessment prior to selecting DES, to maximize the benefits and cost-effectiveness of care, and to improve medication adherence. However, accurate estimation of restenosis risk may require angiographic factors identified at cardiac catheterization.

Methods: In a large PCI registry, we used logistic regression to identify clinical and angiographic predictors of clinically-driven target lesion revascularization (TLR) over the first year after stent placement. Discrimination *c*-statistic and integrated discrimination improvement (IDI) were used to calculate the incremental utility of angiographic variables when added to clinical predictors.

Results: Of 8501 PCI patients, TLR occurred in 4.5%. After adjusting for DES use, clinical TLR predictors were younger age, female sex, diabetes, prior PCI, and prior bypass surgery (model *c*-statistic 0.630). Angiographic predictors were vein graft PCI, in-stent restenosis lesion, longer stent length, and smaller stent diameter (*c*-statistic 0.650). After adding angiographic factors to the clinical model, *c*-statistic improved to 0.680 and the average separation in TLR risk among patients with and without TLR improved by 1% (IDI = 0.010, 95% CI 0.009–0.014), primarily driven by those experiencing TLR (from 5.9% to 6.9% absolute risk).

Conclusions: Among unselected PCI patients, the incidence of clinically-indicated TLR is <5% at 1-year, and standard clinical variables only moderately discriminate who will and will not experience TLR. Angiographic variables significantly improve TLR risk assessment, suggesting that stent selection may be best performed after coronary anatomy has been delineated.

Short summary (for annotated table of contents): Although several recent studies have challenged traditional expectations regarding the duration of dual antiplatelet therapy, current guidelines recommend at least 6 to 12 months of treatment after implantation of a drug eluting stent, with a shorter course for bare metal stents. Stent selection ideally should involve input from the patient receiving these stents, but multiple studies have suggested that angiographic factors – obtained after the patient has received sedation during the diagnostic catheterization – are important predictors of repeat revascularization. In this analysis from a large registry of patients receiving coronary stents, angiographic characteristics were found to significantly improve risk assessment for target lesion revascularization, when added to clinical variables alone.

Abbreviations: BMS, bare-metal stents; CI, 95% confidence interval; DES, drug-eluting stents; EVENT, Evaluation of Drug Eluting Stents and Ischemic Events; HR, hazard ratio; IDI, integrated discrimination improvement; PCI, percutaneous coronary intervention; SVG, saphenous vein graft; TIMI, Thrombolysis In Myocardial Infarction; TLR, target lesion revascularization.

☆ Conflicts of interest: Dr. Stolker reports serving on the speakers' bureau for Astra Zeneca. Dr. Cohen has received research grants from Boston Scientific, Abbott Vascular, Edwards Lifesciences, MedRad, Merck/Schering-Plough, and Eli Lilly-Daiichi Sankyo; he reports serving as a consultant to Schering-Plough, Eli Lilly, Medtronic, and Cordis; and he has served on the speakers' bureau for Eli Lilly, Astra Zeneca, and The Medicines Company. Dr. Kleiman has received research grants from Schering Plough, Boston Scientific, Cordis Corporation, and BMS-Sanofi. Dr. Spertus reports receiving research grant support from Sanofi-Aventis, Bristol Myers Squibb, Lilly, and Amgen. The other authors report no conflicts.

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1. Introduction

Drug-eluting stents (DES) reduce restenosis when compared with traditional bare metal stents (BMS), but patients receiving DES require prolonged antiplatelet therapy to reduce the risk of stent thrombosis and other ischemic events [1,2]. With the cost and higher bleeding rates associated with DES and antiplatelet medications, several recent studies have renewed the debate regarding the magnitude of restenosis reduction provided by DES over BMS [3,4]. These studies are particularly relevant given the lower rates of clinically-driven target lesion revascularization (TLR) demonstrated in real-world practice [5,6], when compared with the landmark clinical trials of DES in more highly selected lesions and patient populations [3,7–9].

Physicians therefore have a need to identify patients at high risk of restenosis who would benefit most from DES, and conversely, those with relatively low restenosis risk (or high risk of medication nonadherence) who may be best served by using BMS. In order to personalize the benefits of TLR reduction using DES in individual patients, risk models have been constructed to help estimate the risk of repeat revascularization after PCI [7,10–13]. Ideally, it would be desirable to involve the patient in this risk:benefit assessment, to maximize the benefits and cost-effectiveness of care, and to improve adherence to dual antiplatelet therapy after PCI. However, accurate estimation of restenosis risk is believed to require angiographic factors [12–17], implying that stent selection for a given patient may be best performed after diagnostic catheterization has been performed. As a result, the informed consent process (where a detailed discussion of DES versus BMS ought to occur) may not be comprehensive until after the diagnostic catheterization, unless pre-procedural characteristics can provide sufficient estimates of DES benefits to discuss stent selection with the patient beforehand.

To evaluate the utility of clinical versus angiographic factors for predicting TLR, we used data from a large multicenter PCI registry to create a TLR risk prediction model for clinical variables available before angiography has been performed. We then quantified the incremental utility of adding angiographic variables for estimating TLR risk, both in the overall patient population and among several prespecified subgroups.

2. Methods

2.1. Patient population

The Evaluation of Drug Eluting Stents and Ischemic Events (EVENT) was a multicenter registry designed to evaluate interventional practice in the DES era [18]. Approximately 50 centers in the United States enrolled unselected patients age 18 and older expected to undergo placement of an intracoronary stent between 2004 and 2007 for any clinical indication. Broadly-inclusive enrollment strategies were employed to minimize selection bias, with PCI or bypass surgery within the past 4 weeks or prior participation in EVENT as the only exclusion criteria. Standard demographic, clinical, and treatment variables were prospectively collected as well as detailed descriptions of medications and cardiac biomarkers. Angiographic characteristics such as lesion complexity and location were determined by the operators at each site. In-hospital clinical events were recorded, and site coordinators contacted patients and/or referring physicians by telephone at 6 and 12 months after the index PCI to identify significant clinical events including hospitalization, myocardial infarction, repeat revascularization, and death. The human studies committee at each site approved the study protocol, and each subject provided written informed consent.

Within EVENT, all patients undergoing PCI with at least one stent (DES or BMS) were eligible for this study. Patients with missing predictor variable data were excluded from the present analysis. Because the informed consent process and clinical decision-making (including selection of DES versus BMS) are approached differently during ST-elevation myocardial infarction, we also excluded patients undergoing primary PCI for this diagnosis. During the time this study was performed, only sirolimus-eluting and paclitaxel-eluting DES were available.

2.2. Data definitions

All follow-up events were reviewed by members of the research team (who were experienced clinical cardiologists), and each repeat revascularization was adjudicated by reviewing the discharge summaries and angiogram reports submitted by each enrolling site. Additional data were obtained from the enrolling hospital when necessary. Patients with missing follow-up data or those who died during follow-up (without first experiencing TLR) were censored at the time of last known event-free contact.

The primary endpoint was defined as TLR occurring during the 12 months after index PCI. TLR included repeat PCI or bypass graft placement for a stenosis in the lesion stented at index PCI, or occurring within 5 mm of the stent ("edge restenosis"), as determined by the investigator at each enrolling site, and then confirmed during the adjudication process.

2.3. Risk model construction

Characteristics of patients experiencing TLR were compared with those not experiencing TLR using chi-square for categorical variables (reported as proportions) and t-tests for continuous variables (reported as mean ± standard deviation). Potential *clinical* predictors of 12-month TLR were selected from candidate variables from prior restenosis literature, and from variables with nominal statistical significance (at $p < 0.1$ level) in the bivariate comparisons from the present study. Candidate variables were sociodemographic factors (age, gender, body-mass index, tobacco use), medical comorbidities (hypertension, diabetes, hyperlipidemia, prior myocardial infarction, prior PCI, prior coronary bypass surgery, heart failure, peripheral arterial disease, glomerular filtration rate), and indication for PCI. We then used logistic regression with backward stepwise elimination (stay criterion $p \leq 0.05$) to identify clinical predictors of TLR with associated hazard ratios (HR) and 95% confidence intervals (CI).

Using the same methodology, we performed a separate analysis to identify the best *angiographic* risk model based on variables obtained from diagnostic coronary angiography. Variables considered were patient-level angiographic characteristics (number of diseased vessels, PCI vessel location, number of lesions and vessels undergoing PCI, total stent number, total stent length) and lesion-specific factors at the stented segment (bifurcation location, in-stent restenosis, TIMI flow grade prior to PCI, lesion severity classification, presence of thrombus prior to PCI, maximal lesion stenosis, minimum stent diameter). In order to account for changing practice patterns during patient enrollment in the EVENT registry, we also adjusted for the date of index PCI in both models. In addition, due to the anticipated reduction in TLR when using DES (versus BMS), we adjusted for DES placement at the index PCI.

2.4. Incremental utility analysis

To evaluate the relative importance of clinical versus angiographic variables for predicting TLR, we first calculated the *c*-statistics separately for the clinical model and for the angiographic model [19]. We then added the angiographic model predictors to the clinical model predictors and calculated the *c*-statistic for the combined TLR risk model, plus the improvement in *c*-statistics and likelihood ratios after adding the new variables [20]. Incremental value was calculated using the integrated discriminatory improvement (IDI) statistic—a measure of change in the separation of predicted probabilities of an event between those with and without events, after adding the second set of variables [21]. Stated another way, the IDI estimates the increase in TLR probability

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