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Comparison of prognostic risk scores after successful primary percutaneous coronary intervention☆

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ABSTRACT

Background: The aim of this study was to compare the predictive ability of clinical risk scores (ACEF, EuroSCORE and EuroSCORE II) to angiographic (SYNTAX score) and combined risk scores (Global Risk Score and Clinical SXscore) towards cardiovascular death and/or major adverse cardiac events (MACE) in patients with ST-segment elevation acute myocardial infarction (STEMI) managed with primary percutaneous coronary intervention (pPCI).

Methods: A total of 685 patients successfully treated with pPCI were evaluated and the risk scores were calculated. The primary endpoint was the 2-year incidence of fatal cardiac events. Secondary end points were target lesion failure (TLF), repeat revascularization (RR) and MACE.

Results: Patients distributed in the highest tertile of EuroSCORE II presented increased rates of CV death (CVD), all-cause mortality and MACE ($p < 0.001$ for all). EuroSCORE II was associated with increased C-statistics (0.873, 95% CIs: 0.784–0.962 and 0.825, 95% CIs: 0.752–0.898 respectively) for predicting CVD and MACE over competing risk scores ($p < 0.05$). EuroSCORE II conferred incremental discrimination (Harrell's C, $p < 0.05$ for all, apart from CSS for predicting CVD) and reclassification value (Net Reclassification Index, $p < 0.05$ for all, apart from CSS for reclassifying MACE) over alternative risk scores for study's main endpoints. EuroSCORE II independently predicted CVD (HR = 1.06, 95% CIs: 1.03–1.09, $p < 0.001$) and MACE (HR = 1.07, 95% CIs: 1.04–1.10, $p < 0.001$).

Conclusion: EuroSCORE II has the best predictive ability of CVD and/or MACE after successful pPCI for the treatment of STEMI.

1. Introduction

Primary percutaneous coronary intervention (PCI, pPCI) has been proven to be the most effective treatment for ST-segment elevation myocardial infarction (STEMI). There are several risk scores for the prediction of the outcome of patients with chronic stable angina or acute coronary syndromes (ACS) undergoing revascularization. SYNTAX (Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery) score (SXscore) is a visual angiographic prognostic model that evaluates lesion complexity, the extent and distribution of coronary atheromatosis and stratifies individual risk [1,2]. However, the absence of clinical factors has led to the creation of a pure clinical model ACEF (age, creatinine, left ventricular ejection fraction (LVEF)). There is a renewed interest in combining clinical and angiographic information to define the risk of patients undergoing revascularization in ACS. So, two combined risk models, the Global Risk Classification (GRS) and the Clinical SYNTAX score (CSS) [3,4] have incorporated clinical variables into the SXscore. The performance of these models has been validated and compared in patients with left main disease undergoing PCI or CABG [5].

The majority of prognostic models that have been applied in STEMI were studied before the widespread application of pPCI [6–11]. Studies evaluating the impact of SXscore on the outcome of patients undergoing pPCI have shown that SXscore predicts better the overall mortality and the incidence of major adverse events in patients with STEMI, but failed to establish an association with cardiovascular (CV) mortality [12].

Several risk scores have been proposed for the outcome after pPCI. Moreover, CCS has been identified as the best combined risk score for the prediction of outcome in patients with successful pPCI [13]. However,

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more recent scores such as EuroSCORE II have not been tested as an outcome predictor in such populations.

EuroSCORE II incorporates 10 patient related factors (age, gender, renal impairment, extracardiac arteriopathy, poor mobility, previous cardiac surgery, chronic lung disease, active endocarditis, critical perioperative state and diabetes on insulin) and 5 cardiac related factors (presence of pulmonary hypertension, left ventricular dysfunction, recent myocardial infarction within 90 days, NYHA and CCS classification). This clinical prognostic score meticulously outlines the most common comorbidities aggregating in patients presenting with STEMI along with haemodynamics (preoperative ventricular tachycardia, ventricular fibrillation/sudden cardiac death, cardiopulmonary resuscitation or intubation) and echocardiographic variables (Supplementary Figure1).

The aim of this study was 1) to validate and compare the performance of EuroSCORE II in patients undergoing successful pPCI towards prediction of CV death and/or major adverse cardiac events (MACE), and 2) to evaluate whether the combined risk models provide additive prognostic information to the ACEF score, the EuroSCORE, EuroSCORE II and the SXscore.

2. Methods

2.1. Study design and sample

This is an observational study; from October 2008 to December 2013, 685 consecutive patients that underwent successful primary PCI due to STEMI in our hospital were recruited out of 703 primary PCIs. Exclusion criteria included: post-arrest primary PCI with or without spontaneous recovery of circulation, administration of thrombolytic agents in the previous 30 days, history of bleeding, major surgery within 15 days, active bleeding or previous stroke within the last 6 months and previous CABG.

Before the procedure, all patients enrolled into the study received 500 mg of acetylsalicylic acid, whereas the 600-mg loading dose of clopidogrel or 60 mg of prasugrel (after coronary anatomy was known) or 180 mg of ticagrelor was only given if no clopidogrel had been administered in the previous 7 days. The use of clopidogrel, prasugrel or ticagrelor was left to the discretion of the operator. 596 (87%) patients received clopidogrel as the second *anti*-platelet agent while in 21 (3.06%) and 68 (9.9%) patients prasugrel (available since 3/2010 in our Hospital) and ticagrelor (available since 5/2011 in our Hospital) were administered respectively. The study protocol was approved by the ethics committee of our institution and all participants signed informed consent. Study has been carried out in accordance with the ethical guidelines of the 1975 Declaration of Helsinki.

All patients were discharged on 100 mg of acetylsalicylic acid indefinitely and clopidogrel 75 mg for at least 1 year or prasugrel 10 mg or ticagrelor 90 mg b.i.d. for the same period. Baseline clinical characteristics and procedural characteristics were recorded in a dedicated electronic database. Successful primary PCI was defined as the presence of TIMI flow 3 after the procedure [14,15]. Out of the 685 patients of the study, 9 patients were in cardiogenic shock and required temporary circulation support (Intra Aortic Balloon Pump). All 9 patients were successfully weaned from Intra Aortic Balloon Pump within the first 48 h post-PCI. One or more 2nd generation Drug Eluting (DES) Stents (Everolimus and Zotarolimus eluting stents) were implanted during the primary PCI. No Bare Metal Stent (BMS) was used in the study population. During the primary PCI, the therapeutic choice for treating only the culprit vessel or all angiographically significant lesions was left on the operator discretion. In cases where only the culprit lesion was stented, complete revascularization for significant coronary stenoses was performed during the indexed hospitalization.

2.2. Scoring systems

The SXscore for each patient was calculated by a team of 2 interventional and experienced cardiologists. All coronary lesions with a diameter stenosis ≥50% in vessels ≥1.5 mm were scored using the SXscore algorithm, which is available on the Web site (www.syntaxscore.com). SYNTAX scoring was performed after wiring or after the use of a small balloon or thrombectomy. The application of predilatation with a balloon, thrombectomy or direct stenting was left to the discretion of the operator. If TIMI flow improved with these measures, this allowed assessment of lesion severity as well as additional disease downstream. Persistence of TIMI 0/1 that did not allow adequate visualization of the lesion was scored as in SXscore I (total occlusion with thrombus) [16]. The investigators that calculated the SXscore were blinded to the patients' clinical characteristics.

The EuroSCORE and EuroSCORE II were calculated on the basis of the original methodology [17,18]. The online interactive calculator of EuroSCORE II is available in *http://www.euroscore.org/calc.htm* The ACEF score was calculated on the basis of the modified formula proposed by Ranucci et al. [19] (i.e., ACEF = [age / left ventricular ejection fraction (LVEF)] + 1 if serum creatinine >2 mg/dl).

The GRS and the CSS were derived as previously described [4,5]. Briefly, the GRS score is a combination of EuroSCORE and SXscore and CSS is a combination of ACEF and Syntax score. Three EuroSCOREII categories were identified by tertiles: LOW ≤ 1.98, MID 1.98 to 3.14 and HIGH ≥ 3.14. Three classes of risk were also grouped by tertiles for the ACEF score (LOW ≤1.28, MID 1.28 to 1.55, HIGH ≥ 1.55), for SXscore (LOW ≤8, MID 8 to 14, HIGH ≥ 14), CSS (LOW ≤11, MID 11 to 20.27, HIGH ≥ 20.27) and for EuroSCORE (HIGH ≤ 5, MID 5 to 8 and HIGH ≥ 8).

2.3. Follow-up

The investigated outcomes included: adverse events (*see* below) that were assessed during hospitalization, as well as at 1, 6, 12 and 24 months after hospital discharge. The follow-up was performed in our outpatient department or by telephone. The primary endpoint was the 2-year incidence of fatal cardiac events (i.e., sudden death, myocardial infarction, or death secondary to heart failure). Deaths were considered cardiac following the ICD-10 definitions. In particular, myocardial infarction was defined according to an extended historical protocol definition and according to Academic Research Consortium (ARC) definitions (18, 19).

Secondary end points were: target lesion failure (TLF), repeat revascularization (RR), stent thrombosis (ST) and major adverse cardiac events (MACE). Specifically, target lesion failure (TLF) was defined as heart attack attributed to the target vessel (target vessel MI), and ischemia-driven target lesion revascularization [20]. Repeat revascularization (RR) was considered as any kind or revascularization (PCI or CABG) in any coronary artery. Percutaneous revascularizations for significant coronary stenoses other than the culprit lesion during the initial hospitalization by definition were not included in the endpoint of "repeat revascularizations". Stent thrombosis (ST) was defined according to the ARC definitions [21]. Major adverse cardiac events (MACE) were defined as the composite of CVD, nonfatal myocardial infarction, or target vessel revascularization.

2.4. Statistical analysis

Data are presented as mean ± SD or absolute and relative frequencies. Continuous variables not following normal distribution are summarized as median (interquartile range). In all patients EuroSCORE II, SXscore, clinical SXscore, EuroSCORE, Euroadditive, ACEF and GRS were calculated. Analyses were stratified according to EuroSCORE II tertiles as the main score of interest. Patients' characteristics pertaining to the primary PCI were compared across EuroSCORE II groups using the analysis of variance (ANOVA) for the normally distributed continuous variables and the chi-square or the Z tests, for categorical variables. The Kolmogorov–Smirnov test as well as P—P plots was used to assess normality.

5-year incidence rates of cardiac mortality were estimated by the Kaplan–Meier method and the log-rank test was used to evaluate differences between tertiles of EuroSCORE II. Data were censored at the time of the last visit. For patients lost during follow-up, their survival data were censored at the last date they were known to be alive. Subsequently, Cox proportional hazard models were fitted to evaluate the predictive ability of the scores on the studied outcomes. The proportional hazard assumption of Cox model was assessed using the appropriate graph and statistical test (Schoenfeld residuals). Associations are presented as hazard ratio (HR) with 95% confidence intervals (CI). Multivariable survival models for main endpoints were built under a bootstrap resampling procedure as previously described [22]. Hundred repeats with forward selection ($P < 0.05$ for selection) and 100 repeats with backward selection [23] ($P < 0.1$ for selection) were performed and variables selected in 80% of all repeats were included in the final multivariable model. Certain variables of biological interest (i.e. gender) were forced to be included in the final models. To avoid overfitting of the multivariable Cox models a ratio of ten events per one confounder incorporated was used as a rule of thumb.

The scores' performances were evaluated in terms of calibration, discrimination and reclassification [24]. Calibration of the multivariable survival models was performed by comparing predicted probabilities and actual observed risk. Improvement in goodness of fit after adding each score to established risk factors was assessed by the likelihood ratio test and the Hosmer–Lemeshow statistic [25]. In terms of discrimination, Receiver Operating Characteristic (ROC) curves were plotted and the corresponding C-statistics were calculated in order to evaluate scores' performance in predicting the outcomes. Comparisons between C-statistic values were performed using the *Z*-test, while the Bonferroni rule for multiple comparisons was applied to control for the inflation of type I error. The incremental predictive value of EuroSCORE II over established risk factors and alternative risk scores was assessed by the Harrell's C-index [26] for censored time-to event data [22] (measure for model discrimination with larger values indicating better discrimination). Harrell's c of inverse hazard ratio was used as a measure of the predictive power of survival regression models estimates and statistics derived with the STATA procedures "somers d" and "lincom" [22].

Finally, to evaluate EuroSCORE's II performance and classification ability we calculated the continuous NRI (cNRI), a category-free version of the NRI [22], and the integrated discrimination index (IDI), which integrates the NRI over all possible cutoffs and is equivalent to the difference in discrimination slopes.

For survival analysis, the final sample size of 685 subjects with survival follow-up data provided over 85% power to establish two-fold alteration in HR (two-sided) for Cox proportional hazards models towards primary endpoint. Type I error was predefined at 0.05. Statistical analysis was performed by STATA package, version 11.1 (StataCorp, College Station, Texas USA). We deemed statistical significance at a = 0.05.

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