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Impact of diabetes on long-term mortality following multivessel percutaneous interventions: An insight into optimal statistical analysis

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ABSTRACT

Background: Several studies have demonstrated better long-term outcomes with drug eluting stents (DES) as compared to bare metal stents (BMS) among diabetics with coronary artery disease (CAD). A significant heterogeneity exists with respect to the optimal statistical strategy to analyze stent related data.
Methods: We used our percutaneous intervention (PCI) registry to identify all diabetics with CAD, who underwent PCI on two or more vessel territories between 2003 and 2009. Long-term mortality was assessed using the social security death index. Six different analytical strategies were applied.
Results: A total of 1568 DES and 336 BMS interventions were encountered in 756 diabetics. Considerable differences were observed in the results between the methods applied. Generalized estimating equation (GEE) approach with an autoregressive correlation structure (GEE) was a robust method to account for the cluster structure, since the measurements taken through time on the same person were assumed to be highly correlated, if they were spaced more closely in time. Diabetics undergoing PCI with BMS had a significantly higher long-term mortality as compared to the patients undergoing DES-PCI [Hazard ratio (95% CI): 1.47 (1.04–2.09)].
Conclusion: There is a great potential for erroneous interpretation of PCI data due to complex spatial and temporal clustering. Use of GEE with autoregressive correlation matrix and robust variance is most optimal to account for the clustered nature of the PCI related data. Using GEE, we observed that there is a 47% (4%–119%) higher hazard for mortality among diabetics undergoing BMS-PCI as compared to diabetics undergoing DES-PCI.

1. Introduction

Approximately 20.8 million people representing 7% of the total US population are currently affected by diabetes [1]. It is projected that about 360 million people will be affected by diabetes worldwide by 2030 [2]. Diabetics have been shown to be at an increased risk for coronary artery disease (CAD) and acute coronary syndromes (ACS) in comparison to non-diabetics [3]. Currently in the US, approximately one-third of the percutaneous interventions (PCI) are done in diabetics [4]. Diabetics undergoing PCI for CAD are at increased risk for death, myocardial infarction (MI), revascularization and stent thromboses as compared to non-diabetics [5–9].

The evidence about the impact of drug-eluting stent (DES) versus bare metal stent (BMS) on long-term mortality among diabetics is divided. A pooled analysis of patients from four trials conducted by Spaulding et al. demonstrated a significantly lower survival rate with DES in comparison to BMS among diabetics [10]. On the contrary, several studies have demonstrated a significant reduction in mortality in diabetics undergoing PCI with DES in comparison to those undergoing PCI with BMS [11,12]. A recent network meta-analysis failed to show any significant difference in rates or death or MI in diabetic patients who received DES versus those who received BMS [13]. There is scarcity of evidence specifically relating to comparison of DES versus BMS in multivessel disease in diabetics.

There is considerable heterogeneity with respect to the optimal statistical strategy to analyze stent-related data. Most patients undergo several interventions on multiple vessel territories, and these procedures are often repeated several times during the course of their disease. This creates a structured correlated matrix of data, and currently there exists no consensus on the optimal method to analyze such data.

With this background, we aim to evaluate various statistical strategies that may be utilized to study the correlated structure of the PCI database. We would use these statistical methods to evaluate the effect of DES versus BMS on long-term mortality among diabetics undergoing multivessel interventions.

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2. Methods

2.1. Study population

The study population was obtained from the PCI database maintained by trained research staff at the Cleveland Clinic. All diabetic patients who underwent concomitant PCI on at least two of the three major vessel territories, excluding the LMCA, were included in the analysis. Patients undergoing PCI for acute ST elevation MI were excluded from the study. The study was approved by the Cleveland Clinic Institutional Review Board.

2.2. Study variables

We retrieved baseline characteristics, cardiac risk factors, angiographic and procedural data along with lesion morphological characteristics including lesion length, eccentricity, tortuosity, calcification, percent stenosis, TIMI flow grade and characteristics of totally occluded lesions and lesions around bifurcations/trifurcations. Using protocols described elsewhere [14], a standardized SYNTAX score for each lesion was calculated. The individual lesion SYNTAX scores were added to generate a cumulative patient SYNTAX score, indicating the complexity of the coronary artery disease in each patient [14]. In addition to the lesion characteristics, we also retrieved the treatment characteristics including stent type, device diameter, device length, post-procedural stenosis and final TIMI flow. The primary outcome was long-term all-cause mortality determined using the social security death index (SSDI).

2.3. Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD) and categorical variables are presented as proportions. Six distinct strategies, as detailed below, were utilized to analyze the data.

2.4. Model 1

This method entailed treating each intervention as a unique entity with identifiable outcome without any consideration for clustering or dependence.

2.5. Model 2

This method utilized non-parsimonious semi-parametric Cox proportional hazard modeling with variance cluster estimation to obtain robust standard errors. There is a certain degree of misspecification in the standard Cox model depicted above, due to existence of within-patient correlation. When we specify variance cluster estimation, the standard errors of the estimated coefficients are valid representation of the sample variability of the coefficients [15].

2.6. Model 3

This method utilized non-parsimonious semi-parametric Cox proportional hazard modeling after choosing one lesion randomly out of all lesions intervened.

2.7. Model 4

This method involved comparison of long-term mortality using Kaplan–Meier survival analysis between the propensity matched DES and BMS groups. The propensity score was calculated for each patient based on logistic regression model incorporating demographic characteristics (age, gender, race), clinical characteristics (BMI, CHF, COPD, stroke, diabetes, hyperlipidemia, hypertension, family history of heart disease, renal failure, smoking, ejection fraction, prior MI) and angiographic characteristics (number of diseased coronary arteries, number of vessels intervened, SYNTAX score). Subsequently, for each patient undergoing BMS-PCI, a patient undergoing DES-PCI with the closest propensity score was chosen to create matched pairs for analysis.

2.8. Model 5

This method involved survival analysis using parametric regression with exponential distribution and gamma-shared frailty. Frailty may be regarded as a random variable that is introduced into the regression model in order to explain the heterogeneity of the model and dependence among multiple event times [16,17]. The most common frailty model assumes frailty from the gamma distribution with mean one and unknown variance [16]. The within-patient correlation is accounted for by utilizing the shared frailty model.

2.9. Model 6

This modeling strategy utilized the generalized estimating equation (GEE) approach with autoregressive correlation structure, robust variance, binomial family and logit link. An autoregressive correlation structure was utilized to account for the cluster structure, since the measurements taken through time on the same person were assumed to be highly correlated, if they were spaced more closely in time. It has been demonstrated that the use of robust variance estimate is associated with minimal impact of covariance assumption on the estimated β coefficients [18].

All effect estimates derived from the respective modeling strategies were calculated using standard bootstrapping with 500 model replicates. For all modeling strategies, each lesion and its corresponding intervention were treated as the smallest unit for statistical analysis. This allowed us to incorporate individual lesion and morphological characteristics, interventional data and post-procedural characteristics into the regression model. The data were analyzed as "clustered data" with multiple lesions in the same person being treated as a single cluster.

All statistical analyses were performed using the statistical software Stata v 10.0 (StataCorp, College Station, TX, USA). All statistical tests were 2-tailed; a p-value <0.05 was considered significant. The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

3. Results

A total of 1568 DES and 336 BMS interventions were encountered in 756 diabetics. The baseline characteristics of the study population are shown in Table 1. A high prevalence of concomitant hypertension, dyslipidemia, history of smoking and prior MI was encountered in our population. The procedure related characteristics are also demonstrated in Table 1. 4.8% of the patients in our study underwent repeat interventions at a later time-point than the index PCI. On an average, each patient underwent PCI on 2.4 lesions. Table 2 demonstrates the differences in lesion characteristics between the lesions intervened using BMS versus those intervened using DES. We observed that the DES treated lesions were significantly longer as compared to the BMS treated lesions. Proportion of calcified lesions and lesions with eccentric stenosis were somewhat higher in patients treated with BMS. The immediate post-intervention results were noted to be similar between the two groups. There were no significant differences in the number of unsuccessful interventions between the two groups. Although the post-procedure stenosis

Table 1
Baseline characteristics.

Characteristic	Value
Number of patients	756
Mean (SD) age	65.4 (10.4)
Males (%)	478 (63.2)
Race (%)	
White	618 (81.8)
Black	90 (11.9)
Other	48 (6.4)
Mean (SD) BMI	32.0 (7.4)
Hypertension (%)	666 (88.1)
Dyslipidemia (%)	704 (93.1)
Stroke (%)	69 (9.1)
Prior history of congestive heart failure (%)	164 (21.7)
Peripheral vascular disease (%)	136 (18.0)
Chronic obstructive pulmonary disease (%)	120 (15.9)
Smoking (%)	
Never	262 (34.7)
Former	396 (52.4)
Current	98 (13.0)
Prior history of myocardial infarction (%)	286 (38.2)
Family history of premature CAD (%)	194 (25.7)
Chronic renal failure (%)	67 (8.9)
Pre-procedure mean (SD) ejection fraction	49.3 (13.2)
Pre procedure NYHA class 3/4 (%)	237 (31.4)
PCI related characteristics	
Number of interventional procedures	792
Repeat interventions (%)	36 (4.8)
Mean (SD) SYNTAX score	11.4 (6.8)
Mean (SD) number of vessels intervened	2.1 (0.3)
Mean (SD) number of lesions intervened at each intervention	2.4 (1.0)
Number of interventions	
Left anterior descending artery	1414 (74.3)
Left circumflex artery	1424 (74.9)
Right coronary artery	1200 (63.0)
Type of interventions	
Drug eluting stents	1568 (82.4)
Bare metal stents	336 (17.6)