


ORIGINAL STUDIES

Percutaneous coronary intervention for left main stem disease: Impact of diabetes mellitus on mortality

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Abstract

Objectives: We assessed the impact of diabetes mellitus (DM) on mortality after percutaneous coronary intervention (PCI) for left main stem (LMS) disease. Second, we compared mortality outcomes between non-insulin treated (NITDM) and insulin treated diabetes (ITDM) in different clinical settings.

Background: There is a paucity of “real world” outcomes data in diabetic patients undergoing LMS PCI.

Methods: We undertook a retrospective analysis of consecutive patients undergoing unprotected LMS PCI at 2 high volume tertiary centers. Diabetic status and clinical setting for PCI were recorded. The primary outcome measure was all-cause 30-day and long-term mortality (up to 36 months) post index PCI.

Results: Between 2003 and 2017, 2,675 patients undergoing index LMS PCI were analyzed. Of those, 77.1% were non-DM, 15.8% NITDM, and 7.1% ITDM. Overall, DM status was not associated with higher 30-day mortality (OR 1.39, 95% CI 0.89–2.16, $p = .15$). During a median follow-up of 36 months, there was a borderline statistical association of DM with long-term mortality in all PCI settings (HR 1.31, 95% CI 1.00–1.71, $p = .05$). Compared to non-DM, ITDM but not NITDM was associated with short- and long-term mortality in all clinical presentations.

Conclusions: Overall, DM did not impact on 30-day mortality and had only a borderline statistical association with long-term mortality. It did not have an influence on mortality in non-emergency LMS PCI. The impact of DM on mortality outcomes following LMS PCI was only significant in the insulin treated patients.

KEYWORDS

diabetes mellitus, left Main Coronary Disease, percutaneous Coronary Intervention

Abbreviations: CABG, coronary artery bypass graft; CAD, coronary artery disease; CS, cardiogenic shock; DM, diabetes mellitus; ITDM, insulin treated diabetes mellitus; LMS, left main stem; MVD, multivessel disease; NSTEMI, non-ST-elevation acute coronary syndrome; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.

1 | INTRODUCTION

Diabetes mellitus (DM) is a recognized predictor of adverse outcomes in patients with coronary artery disease (CAD). Patients with DM have more extensive and complex CAD and have worse outcomes after

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percutaneous coronary intervention (PCI).¹ Revascularisation guidelines for diabetic patients favor CABG in the setting of multivessel disease and left main stem (LMS) disease.² However, dedicated randomized trials in diabetic patients comparing CABG versus PCI have tended to exclude LMS disease^{3,4} and therefore, outcomes data for LMS PCI is lacking.

LMS PCI poses challenges, which are amplified by the presence of DM. Approximately 80% of LMS disease involves the bifurcation, which is associated with a higher risk of restenosis. DM is itself associated with an increased risk of in-stent restenosis due to increased neointimal and smooth muscle cell proliferation.⁵ Furthermore, patients with DM have increased thrombus burden, which is more resistant to standard antithrombotic therapy.⁶ The presence of DM is associated with stent thrombosis,⁷ that in the setting of LMS, is likely to be fatal.

Current advances such as contemporary drug eluting stents, improved intravascular imaging, and potent antiplatelet agents, have improved outcomes after PCI, which is now an established safe and effective option for LMS disease.⁸ The EXCEL trial added credence to the existing revascularization guidelines, which support equipoise between LMS PCI and CABG in low to intermediate anatomical

complexity.⁹ The trial demonstrated noninferiority of contemporary PCI against CABG with respect to the composite end point of death, stroke, or myocardial infarction (MI) for 3 years. Interestingly, the relative treatment effect for the primary endpoint was not affected by DM status, a prespecified subgroup.¹⁰

There is paucity of "real world" long-term (beyond 12 months) outcomes data in diabetic patients undergoing LMS PCI.¹¹ Our study aim was to assess and to compare mortality outcomes following LMS PCI in patients with diabetes versus those without. A secondary aim was to assess mortality in groups stratified according to insulin requirement and to assess the clinical setting of the revascularization procedure.

2 | METHODS

2.1 | Study population

All consecutive patients undergoing unprotected LMS PCI between January 21, 2003 and December 29, 2017 at two high volume

TABLE 1 Baseline clinical and procedure characteristics according to diabetic status

	Non-DM (n = 2063)	DM (n = 612)	p value
Age, mean	68.3	70.3	<.001
Male, n (%)	1,489 (72.2)	420 (68.6)	.088
BMI, mean	27.3	30.2	<.001
Risk factors			
Hypertension, n (%)	1,205 (59.7)	492 (81.2)	<.001
Hypercholesterolemia, n (%)	1,003 (49.6)	400 (66.1)	<.001
Family history, n (%)	944 (49.9)	289 (52.6)	.253
PVD, n (%)	179 (8.9)	104 (17.2)	<.001
Current smoking, n (%)	390 (20.1)	88 (15.4)	.003
Past medical history			
Previous MI, n (%)	636 (31.2)	266 (43.8)	<.001
Previous PCI, n (%)	360 (17.6)	158 (26.1)	<.001
Previous CABG, n (%)	74 (3.6)	53 (8.7)	<.001
CVD, n (%)	156 (7.7)	62 (10.2)	.049
Severe renal disease, n (%)	69 (3.4)	58 (9.5)	<.001
Clinical setting			
Elective, n (%)	651 (31.6)	184 (30.1)	.485
Urgent, n (%)	1,012 (49.1)	338 (55.2)	.007
Emergency, n (%)	400 (19.4)	90 (14.7)	.009
Procedure details			
Radial access, n (%)	1,361 (66.0)	406 (66.3)	.866
Intravascular imaging, n (%)	595 (28.8)	179 (29.2)	.845
MVD, n (%)	82.9 (1709)	91.0 (557)	<.001
MVPCI, n (%)	1,288 (63.0)	411 (67.3)	.056
Stents, n (%)	2020 (97.9)	599 (97.9)	.952
DES, n (%)	1,768 (85.7)	535 (87.4)	.281
Cardiogenic shock, n (%)	169 (8.2)	73 (11.9)	.005

Abbreviations: BMI, body mass index; CVD, cerebrovascular disease; DES, drug eluting stents; DM, diabetes mellitus; MVD, multivessel disease; MVPCI, multivessel PCI; PVD, peripheral vascular disease.

(combined >5,000 PCI procedures/year) tertiary centers in the North East of England were included. The Freeman Hospital, Newcastle Upon Tyne and James Cook University Hospital, Middlesbrough serve a population of >3 million with patients referred from the local area and 12 surrounding district general hospitals.

2.2 | Data collection and study design

Baseline demographics, clinical presentation, and procedure details are prospectively entered into a dedicated PCI database. Data definitions are consistent across both sites and adhere to the National Institute for Cardiovascular Outcomes (NICOR)/British Cardiovascular Intervention Society (BCIS) standard dataset. Data are used for submission to national audit and for quality purposes, including public reporting of the results. Research departments are permitted to use anonymised data for secondary analysis purposes. Mortality data were provided by the Office of National Statistics (ONS) and are routinely linked to the database using NHS patient-unique identification numbers.

The database was retrospectively interrogated for PCI where at least one vessel treated was the LMS. Only index cases during the defined time period were included in the analysis. PCI to ostial left anterior descending (LAD) and/or left circumflex disease with stenting back to LMS were included. Protected LMS PCI and PCI for LMS iatrogenic dissection were excluded. Diabetic status was recorded as nonDM, non-insulin treated DM (NITDM) or insulin treated DM (ITDM). The clinical setting for PCI was recorded as "elective" for patients presenting with stable angina, "urgent" for patients with non-ST-elevation acute coronary syndrome (NSTEMI), and "emergency" for patients with ST-elevation myocardial infarction (STEMI).

2.3 | Outcome measures

The primary outcome measure was all-cause mortality assessed at two time points: 30-days and long-term (up to 36 months) post index PCI. Mortality was assessed up to October 1, 2018 and patient follow-up was censored at this time point or upon death.

2.4 | Statistical analysis

Data are presented as percentages for categorical variables and as means \pm SD or medians and interquartile ranges (25th–75th) for continuous variables. Comparisons between groups were made using chi-square test for categorical variables and one-way ANOVA for continuous variables.

Multiple logistic regression was used to test the impact of DM status on 30-day mortality and adjust for the following confounders selected as per clinical consensus: age, gender, peripheral vascular disease (PVD), previous MI, previous PCI, previous CABG, severe renal disease (defined as Cr 200 μ mol/L or dialysis), multivessel

TABLE 2 Types of stents used

	Non-DM	NITDM	ITDM
Bare metal stents, n (%)	256 (12.6)	50 (12.0)	15 (8.1)
First generation stents, n (%)	201 (9.9)	27 (6.5)	24 (13.0)
Newer generation stents, n (%)	1,567 (77.4)	339 (81.5)	145 (78.8)

Note: First generation stents were Taxus (Boston Scientific) and Cypher (Cordis Corp.) stents. Newer generation stents were mainly Xience (Abbott Vascular), Promus (Boston Scientific), and Resolute Onyx (Medtronic) stents.

Abbreviations: DM, diabetes mellitus; ITDM, insulin treated diabetes mellitus; NITDM, non-insulin treated diabetes mellitus.

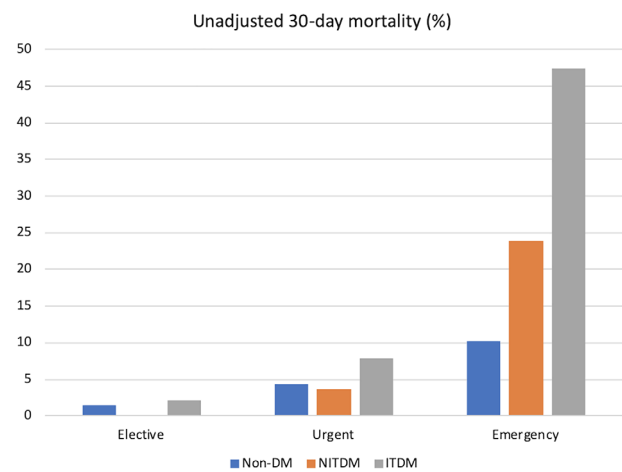


FIGURE 1 Thirty-day mortality according to diabetes subgroups and clinical settings in noncardiogenic shock (CS) patients

TABLE 3 Logistics regression analysis for 30-day mortality in all left main stem (LMS) percutaneous coronary intervention (PCI) cases

	Odds ratio	95% confidence interval	p value
Age	1.04	1.02–1.06	<.001
Male	0.82	0.52–1.29	.39
PVD	1.33	0.77–2.29	.30
Prev MI	1.06	0.68–1.66	.80
Prev PCI	0.57	0.31–1.04	.07
Prev CABG	0.72	0.28–1.89	.51
Renal disease	3.05	1.65–5.63	<.001
Multivessel disease	4.23	1.29–13.90	.02
Diabetes	1.39	0.89–2.16	.15
Femoral access	1.95	1.28–2.95	.002
Multivessel PCI	1.20	0.76–1.89	.43

Abbreviations: CABG, coronary artery bypass graft; MI, myocardial infarction; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease.

disease defined as two or more vessel disease with >50% stenosis, multivessel PCI defined as PCI to two or more vessels and diabetes group. Cardiogenic shock (CS) was excluded in the Kaplan–Meier and sensitivity analyzes due to its overbearing impact on mortality. Goodness of fit for the logistic regression model was assessed using the Hosmer–Lemeshow test and model discrimination by the C-statistic.

Kaplan–Meier survival curves were generated, and the log-rank test was used to assess differences in survival for unadjusted data. Cox proportional hazards regression was used to assess impact of diabetes groups on longer-term mortality following adjustment for aforementioned confounders. A *p* value of less than .05 was considered to indicate statistical significance.

TABLE 4 Odds ratio for 30-day mortality according to diabetic subtype (compared to non-diabetic) stratified to clinical setting

	Adjusted OR (95% CI)		
	DM	NITDM	ITDM
All cases	1.39 (0.89–2.16)	0.98 (0.56–1.73)	2.38 (1.29–4.38)
Urgent	1.11 (0.58–2.11)	0.79 (0.34–1.83)	1.80 (0.75–4.29)
Emergency	4.27 (1.84–9.88)	3.20 (1.21–8.46)	6.09 (1.73–21.41)

Abbreviations: DM, diabetes mellitus; ITDM, insulin treated diabetes mellitus; NITDM, non-insulin treated diabetes mellitus.

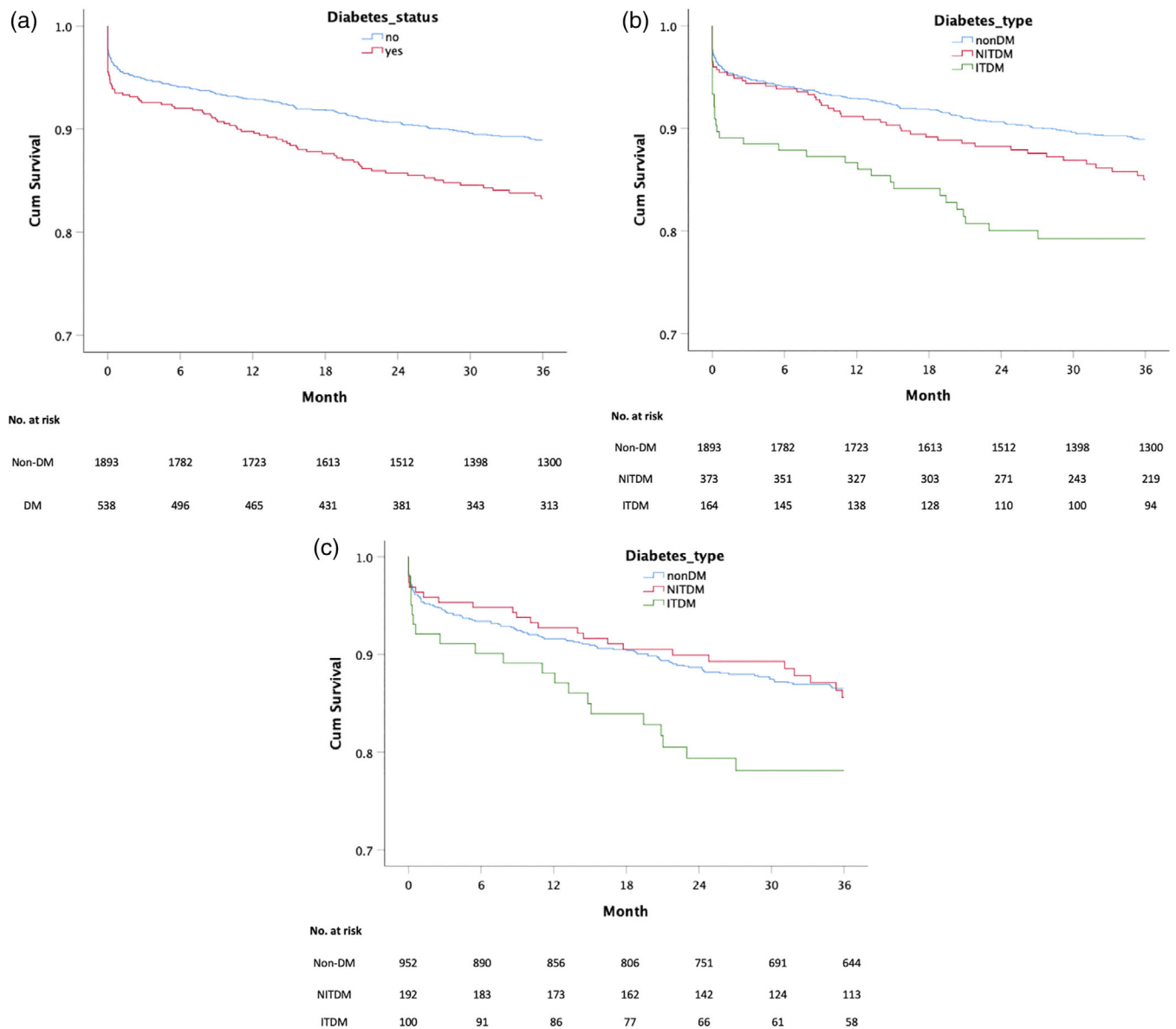


FIGURE 2 Kaplan–Meier curves demonstrating differential mortality according to diabetes mellitus (DM) status (a) DM subtype (b) in all percutaneous coronary intervention (PCI) cases and (c) in urgent cases

3 | RESULTS

3.1 | Study groups, baseline and procedure characteristics

A total of 2,702 patients underwent 2,778 unprotected LMS PCI during the study period. Seventy-six patients underwent repeat interventions to the LMS; only the index procedures were included. Twenty-seven patients were excluded, as their diabetic status was not recorded. Of the remaining 2,675 patients, 2063 (77.1%) were non-DM, 422 (15.8%) NITDM, and 190 (7.1%) ITDM.

Table 1 shows the baseline clinical and procedural characteristics according to the diabetic status. Differences between non-DM, NITDM, and ITDM are shown in Table A in Appendix section. Patients with DM had a higher burden of cardiovascular risk factors, previous MI, and prior revascularization. This group was also characterized by higher risk PCI features including severe renal disease, multivessel (MVD) disease, and CS. Half of the cases were urgent PCI for NSTEMI-ACS. We found no significant difference in intravascular imaging use between DM and non-DM. The majority of patients received newer generation stents (Table 2).

3.2 | Thirty-day mortality

Overall 30-day mortality was 209/2675 (7.8%). Mortality in patients with and without CS was 93/242 (38.4%) and 116/2433 (4.8%), respectively. Figure 1 demonstrates 30-day mortality according to diabetes subgroups and clinical indications in non-CS patients. Mortality was highest in ITDM undergoing emergency PCI. In a logistic regression model including all LMS PCI excluding CS cases, DM status was not associated with 30-day mortality (OR 1.39, 95% CI, $p = .15$). The following were independent predictors: age, renal disease, MVD, and femoral access (Table 3). The logistic model showed good discrimination and fit (C-statistic 0.72, Hosmer–Lemeshow p value = .575). When analyzing DM subgroups, ITDM was significantly associated with 30-day mortality in all settings (Table 4). ITDM and NITDM showed significant associations in the emergency but not the urgent setting. Regression analyses were not performed in the stable angina group due to low event rates.

3.3 | Long-term mortality

During a median follow-up of 36 months, Kaplan–Meier curves demonstrate that patients with DM had higher mortality than non-DM (Log Rank test $p = .001$, Figure 2a). Compared to non-DM, patients with NITDM had similar mortality ($p = .052$) while patients with ITDM had significantly higher mortality ($p < .001$) (Figure 2b). A similar pattern was observed in patients undergoing urgent PCI, the largest group studied (Figure 2c). Cox regression analysis showed that there was a borderline statistical association of DM with long-term mortality in all PCI settings (HR 1.31, 95% CI 1.00–1.71, $p = .05$). Other independent predictors were age, PVD, previous MI, renal impairment, MVD, and femoral access (Table 5). Compared to non-DM, ITDM but not NITDM was associated with long-term mortality in all PCI cases (Table 6). All DM subtypes were significant predictors of poor outcome in PPCI to LMS in STEMI. The impact of DM on long-term mortality was not significant when stratified to 3 “PCI eras” (2003–2007, 2008–2012, 2013–2017) (Table B in Appendix).

TABLE 5 Cox regression analysis for 3-year mortality in all PCI cases

	Hazards ratio	95% confidence interval	p value
Age	1.03	1.02–1.04	<.001
Male	0.84	0.64–1.11	.84
PVD	1.56	1.14–2.13	.005
Prev MI	1.85	1.42–2.40	<.001
Prev PCI	0.56	0.39–0.78	<.001
Prev CABG	0.57	0.32–1.04	.07
Renal disease	2.93	2.05–4.20	<.001
Multivessel disease	1.80	1.10–2.95	.02
Diabetes	1.31	1.00–1.71	.05
Femoral access	1.53	1.19–1.97	.001
Multivessel PCI	0.91	0.70–1.18	.47

Abbreviations: CABG, coronary artery bypass graft; MI, myocardial infarction; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease.

TABLE 6 Hazards ratio for long-term mortality according to diabetic sub-type (compared to non-diabetic) stratified to clinical setting

	Adjusted HR (95% CI)		
	DM	NITDM	ITDM
All cases	1.31 (1.00–1.71)	1.21 (0.89–1.66)	1.54 (1.02–2.31)
Elective	1.75 (0.90–3.39)	1.91 (0.95–3.82)	1.25 (0.35–4.40)
Urgent	1.05 (0.74–1.50)	0.91 (0.59–1.41)	1.35 (0.81–2.24)
Emergency	2.29 (1.30–4.01)	2.14 (1.13–4.05)	2.69 (1.12–6.44)

Abbreviations: DM, diabetes mellitus; ITDM, insulin treated diabetes mellitus; NITDM, non-insulin treated diabetes mellitus.

4 | DISCUSSION

Our analysis of patients treated with LMS PCI showed that DM status was not an independent predictor of 30-day in the non-emergency setting. It had only a borderline statistical association with long-term mortality.

When considering DM subtypes, ITDM but not NITDM was associated with mortality, with the greatest impact in the emergency setting—a finding reported previously in a large series of patients undergoing PCI to any vessel.¹² We can speculate that the higher burden of cardiovascular risk factors such as PVD and renal disease, multivessel disease and low usage of radial access may have contributed to the increased mortality seen in the ITDM group.

Previous studies have shown that DM adversely affects outcomes following PCI.^{13,14} However, our study showed a differential impact on mortality dependent on DM type. This may be the result of significant improvement in risk factor control, leading to the reduction of CAD risk in diabetes.¹⁵ The rates of diabetes-related macrovascular complications have also reduced significantly in the past two decades.¹⁶ Secondary preventative strategies continue to evolve with SGLT2 inhibitors demonstrating a significant reduction in major adverse cardiac events in Type 2 DM with established CAD.¹⁷

Left main stem disease is associated with significant myocardial jeopardy and CABG has historically been the preferred revascularization modality. In diabetic patients requiring revascularization, CABG with an internal mammary graft to the left anterior descending artery, has been associated with lower mortality compared with PCI in the setting of complex multivessel disease in randomized controlled trials.^{4,18} Current guidelines recommend CABG as the standard of care for diabetic patients with CAD of intermediate to high SYNTAX scores including in the setting of LMS disease.² However, DM was not an independent predictor of events once the SYNTAX score was entered in the multivariable model.¹⁹ Consequently, DM is excluded in the SYNTAX 2 score that helps determine the preferred revascularization strategy.²⁰ In a pooled analysis of three randomized trials comparing CABG versus PCI in patients with DM and low or intermediate anatomic complexity (SYNTAX less or equal to 32), both groups had similar 5-year rates of all-cause death, cardiac death, and the composite of death, MI, or stroke.²¹

With contemporary interventional technology, there is increasing evidence that LMS PCI is a comparatively effective and safe strategy. A prespecified subgroup analysis of the EXCEL trial¹⁰ reported rates of a 3-year primary endpoint to be similar after treatment with PCI and CABG in diabetic (20.7% vs. 19.3%) and in non-diabetic patients (12.9% vs. 12.9%). Importantly, DM status showed no significant interaction effect with CABG and PCI in establishing short- and long-term outcomes suggesting that DM status is not a critical determinant of the mode of revascularization strategy in LMS disease.

In our study, DM status, as a dichotomous variable, did not impact on early or late mortality. The morbidity associated with DM such as PVD, MVD, and renal disease were independent predictors of mortality. Increasing evidence suggesting that the presence of DM should not be a factor in determining revascularization strategy

(PCI vs. CABG) for LMS disease, which is supported by data from our study. In the absence of significant vascular complications, diabetic patients on diet or oral hypoglycemic have similar outcomes to non-diabetic patients. However, in patients on insulin treatment, there is an increased mortality risk especially after ST-elevation MI.

5 | LIMITATIONS

Our primary data source is the BCIS database. While data are entered prospectively and audited, it does not capture all the clinical variables that can impact on prognosis. We do not have information about significant non cardiac comorbidities. Left ventricular function was recorded in less than 40% patients and therefore was missing from analysis. A comprehensive anatomical evaluation is not available and SYNTAX score is not routinely documented. We have defined MVD as a minimum of two non-LMS epicardial coronary stenoses >50% in an attempt to differentiate isolated LMS disease (LMS shaft or bifurcation) against LMS disease with more complex disease pattern. Our data shows that MVD is an important predictor of mortality. In our institutions, patients with nonemergency presentations and significant LMS disease are discussed in a heart team. Our database captures a heterogeneous group of patients undergoing LMS PCI after clinical presentation, co-morbidities, anatomical complexity, and patient preference have all been considered. We do not have information about medical therapy following PCI. In both centers, the following dual antiplatelet guidelines are practiced: in addition to long-term aspirin, elective patients receive 12 months of clopidogrel; NSTEMI-ACS, 12 months of ticagrelor and STEMI, 12 months of ticagrelor or prasugrel. Of note, prasugrel and ticagrelor were in use after 2009. Finally, we do not have follow-up data for MI and repeat revascularization or outcomes beyond 3 years.

6 | CONCLUSIONS

Our data in a large real-world cohort of patients showed that DM did not impact on 30-day mortality and had only a borderline statistical association with long-term mortality over a 3 year follow-up period. It did not have an influence on mortality in non-emergency LMS PCI. This is in accordance with the contemporary evidence from clinical trials of LMS PCI showing equipoise between percutaneous and surgical revascularization strategies. We also showed that non-insulin treated DM did not affect short- and long-term mortality when adjusted for other confounders. A consistent finding from other studies was also replicated in this registry and confirmed that increased mortality following LMS PCI in DM patients was only present in insulin treated patients. Our data provides both, a cautionary note for LMS PCI in the insulin treated patients and evidence for future studies to focus on these patients.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Bawamia BR, Egred M, Jackson M, Purcell I, Austin D, Zaman AG. Percutaneous coronary intervention for left main stem disease: Impact of diabetes mellitus on mortality. *Catheter Cardiovasc Interv*. 2020;96: E416-E422. <https://doi.org/10.1002/ccd.28818>