Predictors of 30-day and 12-month mortality in left main stem percutaneous coronary intervention 2016-2020: A study from two UK centres

Elliott J Carande[1*], Majd B Protty[2*], Sarah Verhemel[3], Mohammed H Hussein[1], Ajay Sundara Raman[1], Zia UlHaq[1], Shantu Bundhoo[3], James Cullen[3], Adrian Ionescu[1], Anirban Choudhury[1], Hussain I Hussain[3], Ahmed Hailan[1]

[1]Department of Cardiology, Morriston Cardiac Centre, Swansea, UK
[2]Systems Immunity University Research Institute, Cardiff University, Cardiff, UK
[3]Department of Cardiology, The Grange University Hospital, Cwmbran, UK

*Joint first co-authors

Corresponding Author:

Dr. Ahmed Hailan

Consultant Interventional Cardiologist

Department of Cardiology,

Morriston Cardiac Centre,

Swansea, UK

Email: Ahmed.hailan@wales.nhs.uk

Phone: +44 1792 704124

Brief title: Predictors of mortality in left main stem PCI

Keywords: left main stem; percutaneous coronary intervention; outcomes; complex coronary angioplasty

Conflicts of interest: No conflicts of interest for any authors, no relevant relationship with industry

Word count: 3,423 (including references and abstract)

Abstract

Introduction: Left main stem percutaneous coronary intervention (LMS-PCI) is a complex high-risk procedure which can be performed as an alternative to coronary artery bypass graft (CABG) procedure in surgical turn-down patients or where there is equipoise in percutaneous versus surgical strategies. Current guidelines suggest that PCI is an appropriate alternative to CABG in patients with unprotected LMS disease and low SYNTAX score. However, 'real world' data on outcomes of LMS-PCI remain limited. This study aims to quantify and determine predictors of mortality following LMS-PCI.

Methods: Using local coronary angioplasty registries from two UK centres, all LMS-PCI cases were identified from 2016-2020. Descriptive statistics and multivariate logistic regressions were used to examine the association between baseline and procedural characteristics with 30-day and 12-month mortality.

Results: We identified 484 cases of LMS-PCI between 2016 and 2020. There was a year-on-year increase in the number of LMS-PCI, the highest being in 2020. Covariates associated with higher 30-day mortality were age (OR 1.07, 95% CI: 1.02-1.12) and shock pre-procedure (OR 23.88, 95% CI: 7.90-72.20). Covariates associated with higher 12-month mortality were age (OR 1.04, 95% CI: 1.01-1.08), acute coronary syndrome (OR 2.50, 95% CI: 1.08-5.80), renal disease (OR 5.24, 95% CI: 1.47-18.68) and shock pre-procedure (OR 7.93, 95% CI: 3.30-19.05). Overall, 30-day and 12-month mortality in this contemporary dataset were 9.5% and 16.7%, respectively, with significantly lower rates in elective cases ($p<0.01$).

Conclusions: Older age and cardiogenic shock pre-procedure were associated with increased 30-day mortality after LMS-PCI. 12-month mortality was associated with older age, ACS presentation, pre-existing renal disease and cardiogenic shock pre-procedure.

WHAT IS KNOWN:

- Left main stem percutaneous coronary intervention (LMS-PCI) is a complex high-risk procedure which is increasingly utilised in cases where there is surgical turn-down or equipoise in percutaneous versus surgical strategies.
- However, contemporary data on its outcomes in real-life practice remain limited.

WHAT THE STUDY ADDS:

- In databases from two UK PCI centres, LMS-PCI volumes have been increasing since 2016 to 2020.
- Covariates associated with higher 12-month mortality include older age, acute coronary syndrome presentation, renal disease and shock pre-procedure.
- Overall mortality from LMS-PCI in this real-life registry was at 9.5% (30 days) and 16.7% (12 months). However, this was significantly less in elective cases compared with acute cases (3.3% vs 12.3% at 30 days, $p < 0.01$)

INTRODUCTION

Left main stem coronary artery disease occurs in 3% to 5% of patients with coronary artery disease[1,2] and is associated with high morbidity and mortality[3]. Early studies demonstrated coronary artery bypass grafting (CABG) for patients with left main stem disease improved survival compared with medical treatment alone[4,5] . Consequently, CABG was considered the gold standard of care for patients with left main stem disease in previous European Society of Cardiology (ESC) guidelines[6].

More recently, randomised control trials investigating the role of left main stem percutaneous coronary intervention (LMS-PCI) compared to CABG showed similar rates of death and myocardial infarction (MI) at 12-months between the two groups in the SYNTAX study[7], and showed non-inferiority of LMS-PCI compared to CABG in patients with low to intermediate anatomical complexity for death, stroke or MI at 3 years in the EXCEL study[8].

A further randomised control trial, the NOBLE study[9], found that there was similar mortality between LMS-PCI and CABG treatment arms, but higher rates of MI and repeat revascularisation in the LMS-PCI group. Given the results of these studies, the ESC/European Association for Cardio-Thoracic Surgery (EACTS) 2018 guidelines[10] report that "PCI is an appropriate alternative to coronary artery bypass surgery in unprotected left main stem disease of low-to-intermediate anatomical complexity". Class I recommendation is given for both CABG and PCI in patients with low SYNTAX score (0-22) due to similar clinical outcomes, whilst there is a Class II recommendation for PCI in patients with intermediate anatomical complexity (SYNTAX score 23-32).

What remains lacking however is ‘real world’ outcome data on LMS-PCI, particularly as they relate to hard outcome such as mortality. This study investigates the frequency of performing LMS-PCI from contemporaneous two-centre data and quantify the incidence of death at 30-days and 12-months after procedure, and the risk factors associated with increased mortality.

METHODS

Study participants

This was a retrospective analysis of local PCI registries from two centres in the United Kingdom between Jan 2016 to Dec 2020. All LMS-PCI cases were identified and included in this study. The study design was approved by local clinical governance procedures as quality improvement measures.

The local PCI registries are designed in line with the guidelines from the national institute of cardiovascular outcomes research (NICOR) and the British cardiac intervention society (BCIS) to inform patients and the public on PCI outcomes in UK national health service (NHS) centres.[11] UK interventional cardiologists are mandated to enter all the PCI procedures, including complications, onto these datasets as part of professional revalidation.

Design of the study

Using the above datasets, data on LMS-PCI cases obtained included age, gender, smoking history (current or ex-smoker), pre-procedural renal failure (defined as creatinine >200µmol/l, renal transplant history, or dialysis), diabetes mellitus, previous PCI to any vessel, previous coronary artery bypass grafting (CABG), family history of coronary artery disease (CAD), Q wave on ECG, out of hospital cardiac arrest (OOHCA), New York Heart Association (NYHA) score, Canadian Cardiovascular Society (CCS) score, acute coronary syndrome (ACS) status, use of microcatheter, cutting balloon, rotablation (rotational atherectomy), intravascular lithotripsy (IVL), drug eluting balloons (DEB), intravascular imaging (both intravascular ultrasound, IVUS, and optical coherence tomography, OCT), access site, use of pressure wire, target vessel for PCI, no of stents used, and complications of side branch loss, dissection, shock induced by procedure, perforation, slow flow, DC cardioversion (DCCV) and death at 30 days and 12 months.

Statistical analyses

Statistical analysis was performed using the R coding environment (Open Source). Multiple imputations were carried out using the *mice* package to reduce the potential bias from missing data (**Supplementary Table S1**), assuming missingness at random mechanisms. We used chained equations to impute the data for all variables with missing information and generated 5 datasets to be used in the analyses. We examined co-variates associated with 30-day and 12-month mortality. We explored crude baseline comorbidities using a Chi-squared test for categorical variables and the Wilcoxon-Mann-Whitney test for continuous variables.

RESULTS

Baseline characteristics of LMS-PCI cases included in the study

Throughout the study period, 484 LMS-PCI cases were performed across the two centres, from a total of 9480 (5.1%) PCI procedures. Crude numbers per year of LMS-PCI increased during the study period from 46 (2.5% of total PCI) in 2016 to 167 (8.7% of total PCI) in 2020. The baseline characteristics of LMS-PCI patients overall and per year is presented in **Table 1**. There was a significantly increasing number of cases with a previous PCI to any vessel and family history of CAD ($p<0.05$). In contrast, there was a significant decline in the number of cases with OOHCA and pre-procedural shock over the study period ($p<0.05$).

Procedural characteristics of LMS-PCI cases

Over the study period, there was a higher use of microcatheters, cutting balloons, IVL, intracoronary imaging use (74.3% in 2020), concurrent PCI to proximal LAD, other LAD and three-vessels with a higher mean number of stents used (**Table 2**, $p<0.05$). The proportion of ACS cases undergoing LMS-PCI reduced over the study period from 84.8% to 69.5% (**Table 2**, $p<0.05$). These trends likely reflect increased uptake of contemporary enabling strategies, that is intravascular imaging, physiological indices, microcatheters, atherectomy devices or lesion-modifying balloons such as scoring/cutting balloons, with an increase in the number of stable LMS-PCI cases.

Clinical outcomes of LMS-PCI

The unadjusted outcomes of LMS-PCI overall and per year are presented in **Table 3**. These demonstrate a 2.7% risk of dissection, 0.6% shock induction, 0.2% coronary perforation, 1.0% slow flow, 0.4% DCCV and 0.8% side branch loss. Real world mortality rates were recorded at 9.5% (30-days) and 16.7% (12-months) with no significant change over the study period.

Multivariate logistic modelling of 30-day mortality and 12-month mortality was used to adjust outcomes for baseline and procedural comorbidities. This showed that 30-day mortality was associated with older age (OR 1.07, 95% CI: 1.02-1.12) and shock pre-procedure (OR 23.88, 95% CI: 7.90-72.20), as shown in **Figure 1**. Co-variates associated with higher 12-month mortality are presented in **Figure 2**, demonstrating lower odds of 12-month mortality for patients undergoing concurrent right coronary artery (RCA) PCI (OR 0.23, 95% CI: 0.06-0.86) but higher risk of 12-month mortality with advancing age (OR 1.04, 95% CI: 1.01-1.08), ACS presentation (OR 2.50, 95% CI: 1.08-5.80), pre-existing renal disease (OR 5.24, 95% CI: 1.47-18.68) and shock pre-procedure (OR 7.93, 95% CI: 3.30-19.05).

Finally, given the independent association of ACS with mortality in the adjusted model, we re-analysed baseline, procedural and outcome characteristics of the cohort by ACS status (elective/acute). Indeed, there were significantly lower rates of unadjusted mortality in elective cases compared with acute cases both at 30 days and 12 months (**Supplementary Table S2**).

DISCUSSION

We showed that there was a 9.5%, and a 16.7%, at 30-day and 12-month mortality, respectively, in this patient group. 30-day mortality was similar to a recent study of in-hospital outcomes for patients undergoing LMS-PCI in all New Zealand PCI centres, which demonstrated an in-hospital mortality of 7.9%[12]. This study was similar for including all LMS-PCI cases and had similar characteristics of patients with regards to age, diabetes and previous PCI. This study demonstrated the use of intra-aortic balloon pump in 10% of cases. No data was provided regarding operator volume.

A further recent study from the British Cardiovascular Intervention Society Database for all UK centres showed slightly lower 30-day mortality after LMS-PCI between 2.9% and 6.6%, and similar 12-month mortality between 9.0% and 15.5%[13]. This UK study investigated all *unprotected* LMS-PCI, but had similar levels of procedural complexity, but with slightly lower levels of circulatory support during PCI (6%) than the previous study.

This is higher than the risk for standard all-comer PCI, and therefore, there is a mandate that the risks are clearly communicated to patients undergoing LMS-PCI in this setting. Nevertheless, mortality rates were significantly lower in elective compared with acute cases at both 30 days and 12 months (Supplementary Table S2). This therefore may influence the operators' decision with respect to timing of the intervention, akin to the approach of cardiac surgeons to elective versus urgent CABG, where the former is associated with lower mortality rates[14].

The relatively high mortality rates demonstrated in this study reflect the high-risk patient population under investigation, with many cardiovascular risk factors, and who may be unsuitable for CABG. This study had a high proportion of patients with underlying diabetes mellitus, with average age >70 years, as well as significantly increasing number of cases throughout the study with previous PCI to any vessel and family history of CAD (**Table 2**). Therefore, LMS-PCI cases became more complex over time in regards to previous PCI, although we found a significant reduction in cases presenting in out of hospital cardiac arrest (OOHCA) and pre-procedural shock. Despite there being no significant increase in the number of patients with diabetes throughout the study, this still represented a high proportion (27.6%) of patients.

Throughout the course of our study, we have noted an increase in the use of contemporary enabling strategies (microcatheters, cutting balloons, IVL, and intracoronary imaging use). However, we did not find a significant reduction in dissection, or coronary perforation over the same time period.

In this study, we demonstrated that age and pre-procedural cardiogenic shock were significant risk factors for 30-day mortality and that age, ACS presentation, renal disease and pre-procedural shock were significant risk factors for 12-month mortality. A study of patients presenting with STEMI requiring LMS-PCI[15] found that older age is a risk factor for in-hospital mortality, similar to our study analysing 30-day mortality, and also found increased risk of in-hospital mortality for patients with diabetes mellitus, and absence of post-PCI thrombolysis in myocardial infarction (TIMI) 3 flow. A further study performed in the LMS-PCI group demonstrated that STEMI, femoral access, and worse renal function were independent risk factors of in-hospital mortality[12].

Concerning predictors for 12-month mortality, previous data supports our findings that age was a risk factor for 12-month mortality (in STEMI, non-ST elevation ACS (NSTEACS) and chronic stable angina patient groups), as well as pre-procedural cardiogenic shock (STEMI and NSTEACS patients only) and chronic renal failure (NSTEACS patients only)[16]. This data is supported by previous studies which have demonstrated that cardiogenic shock in the context of acute myocardial infarction is a poor prognostic factor, with in-hospital mortality between 27-51%.[17]

There was a significant association between concurrent RCA PCI and reduced mortality at 12-months. Other studies have also reported this finding, where patients with concomitant PCI to RCA lesions during the same hospitalisation as LMS-PCI reduced 30-day cardiovascular death and 3-year RCA revascularisation rate.[18] This was supported by previous data that incomplete revascularisation in multiple vessel disease increased the risk of death, MI, and repeated revascularisation.[19]

The protective effect of RCA PCI may reflect improved perfusion of the myocardium by RCA PCI[20], leading to better outcomes from LMS PCI performed concurrently. Another possibility for this effect may be that this reflects technically easier cases, enabling operators to carry out two-vessel PCI in same sitting, leading to more favourable outcomes.

Guidelines currently recommend that "PCI is an appropriate alternative to coronary artery bypass surgery in unprotected left main stem disease of low-to-intermediate anatomical complexity".[10] Therefore, SYNTAX score may be used for guiding revascularisation strategies in this patient group in terms of inclusion and exclusion for PCI. In addition to SYNTAX, the location of the LMS disease (ostial, mid, distal) may influence the strategy used for revascularisation or stenting, particularly where it implicates the LAD/Cx bifurcation.[21] Whilst these variables are not routinely collected in this dataset, it is likely that the outcomes of LMS PCI may be influenced by them. Nevertheless, over the course of the study period, we noted an increase in the use of intracoronary imaging and angioplasty devices. Recent evidence[13] has demonstrated the role in intravascular ultrasound (IVUS) imaging in LMS-PCI, leading to lower rates of coronary complications, in-hospital major adverse cardiac events, and improved 30-day, and 12-month, mortality. We did not find that IVUS led to statistically significant improved mortality at either timepoint, but we note a signal towards benefit at the 30-day mortality timepoint. Given the small numbers in our study, this signal may not be real and would require investigation in larger studies/registries.

All patients received dual anti-platelet therapy in line with European Society of Cardiology (ESC) guidelines, either 12-months for ACS, 6-months for stable disease, or reduced if there was concurrent use of anti-coagulation.[22]

We note some limitations within the study. Firstly, the database does not record SYNTAX score or bifurcation PCI technique and therefore we are unable to provide any further conclusions to the impact of these variables on LMS-PCI outcome. Secondly, the location and cause of complications (detailed in **Table 3**) is not distinguished by our database. Thirdly, outcomes from CABG from the two centres were not available for comparison of mortality between revascularisation strategies, albeit a true comparison may not be possible due to differences in patient characteristics. We also note that our study was limited to two centres and therefore may not be representative of all centres in the UK.

Finally, despite aiming to correct for baseline differences, the observational and retrospective nature of our study may still have unmeasured confounders such as frailty or technical difficulties. Consequently, conclusions need to be interpreted in the context of the nature of the study design.

CONCLUSIONS

LMS-PCI was performed in a high-risk cohort of patients across two UK PCI centres, demonstrating that 30-day mortality after LMS-PCI was associated with older age and cardiogenic shock pre-procedure, and 12-month mortality was associated with older age, ACS presentation, pre-existing renal disease and cardiogenic shock pre-procedure. Concurrent RCA PCI had a protective effect on 12-month mortality. There were lower mortality rates in elective versus acute cases at both 30 days and 12 months. Awareness of the high-risk of mortality in this patient group should be used for appropriate patient selection and procedural consent.

CONFLICTS OF INTEREST

There are no conflicts of interest for any authors relevant to this work.

STUDY FUNDING

There was no funding provided for this study.

REFERENCES

1. Ragosta, M., Dee, S., Sarembock, I. J., Lipson, L. C., Gimple, L. W. & Powers, E. R. Prevalence of unfavorable angiographic characteristics for percutaneous intervention in patients with unprotected left main coronary artery disease. *Catheter. Cardiovasc. Interv.* **68**, 357–362 (2006).
2. Buszman, P. E., Buszman, P. P., Kiesz, R. S., *et al.* Early and long-term results of unprotected left main coronary artery stenting: the LE MANS (Left Main Coronary Artery Stenting) registry. *J. Am. Coll. Cardiol.* **54**, 1500–1511 (2009).
3. Stone, G. W., Sabik, J. F., Serruys, P. W., *et al.* Everolimus-Eluting Stents or Bypass Surgery for Left Main Coronary Artery Disease. *N. Engl. J. Med.* (2016) doi:10.1056/NEJMoa1610227.
4. Fisher, L. Coronary artery surgery study (CASS): a randomized trial of coronary artery bypass surgery. Survival data. *Circulation* **68**, 939–50 (1983).
5. Varnauskas, E. Twelve-year follow-up of survival in the randomized European Coronary Surgery Study. *N. Engl. J. Med.* **319**, 332–7 (1988).
6. Silber, S., Albertsson, P., Avilés, F. F., *et al.* Guidelines for percutaneous coronary interventions. The Task Force for Percutaneous Coronary Interventions of the European Society of Cardiology. *Eur. Heart J.* **26**, 804–47 (2005).
7. Serruys, P. W., Morice, M.-C., Kappetein, A. P., *et al.* Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N. Engl. J. Med.* **360**, 961–72 (2009).
8. Stone, G. W., Sabik, J. F., Serruys, P. W., *et al.* Everolimus-Eluting Stents or Bypass Surgery for Left Main Coronary Artery Disease. *N. Engl. J. Med.* **375**, 2223–2235 (2016).
9. Mäkikallio, T., Holm, N. R., Lindsay, M., *et al.* Percutaneous coronary angioplasty

versus coronary artery bypass grafting in treatment of unprotected left main stenosis (NOBLE): a prospective, randomised, open-label, non-inferiority trial. *Lancet* **388**, 2743–2752 (2016).

10. Neumann, F. J., Sousa-Uva, M., Ahlsson, A., *et al.* 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur. Heart J.* **40**, 87–165 (2019).

11. Ludman, P. F. British Cardiovascular Intervention Society Registry for audit and quality assessment of percutaneous coronary interventions in the United Kingdom. *Heart* **97**, 1293–1297 (2011).

12. Wang, T. K. M., Kerr, A., Kasargod, C., *et al.* Percutaneous Coronary Intervention for Left Main Coronary Disease in New Zealand: National Linkage Study of Characteristics and In-Hospital Outcomes (ANZACS-QI 38). *Cardiovasc. Revascularization Med.* **21**, 573–579 (2020).

13. Kinnaird, T., Johnson, T., Anderson, R., *et al.* Intravascular Imaging and 12-Month Mortality After Unprotected Left Main Stem PCI: An Analysis From the British Cardiovascular Intervention Society Database. *JACC Cardiovasc. Interv.* **13**, 346–357 (2020).

14. Kurki, T. S., Kataja, M. & Reich, D. L. Emergency and Elective Coronary Artery Bypass Grafting: Comparisons of Risk Profiles, Postoperative Outcomes, and Resource Requirements. *J. Cardiothorac. Vasc. Anesth.* **17**, 594–597 (2003).

15. Yap, J., Singh, G. D., Kim, J. S., *et al.* Outcomes of primary percutaneous coronary intervention in acute myocardial infarction due to unprotected left main thrombosis: The Asia-Pacific Left Main ST-Elevation Registry (ASTER). *J. Interv. Cardiol.* **31**, 129–135 (2018).

16. Almudarra, S. S., Gale, C. P., Baxter, P. D., *et al.* Comparative outcomes after unprotected left main stem percutaneous coronary intervention: A national linked

cohort study of 5,065 acute and elective cases from the BCIS registry (British Cardiovascular Intervention Society). *JACC Cardiovasc. Interv.* **7**, 717–730 (2014).

17. Van Diepen, S., Katz, J. N., Albert, N. M., *et al. Contemporary Management of Cardiogenic Shock: A Scientific Statement from the American Heart Association*. *Circulation* vol. 136 (2017).
18. Lee, C. H., Chong, S. Z., Hsueh, S. K., Chung, W. J. & Cheng, C. I. Residual Right Coronary Artery Stenosis after Left Main Coronary Artery Intervention Increased the 30-Day Cardiovascular Death and 3-Year Right Coronary Artery Revascularization Rate. *J. Interv. Cardiol.* **2020**, (2020).
19. Nagaraja, V., Ooi, S. Y., Nolan, J., *et al.* Impact of incomplete percutaneous revascularization in patients with multivessel coronary artery disease: A systematic review and meta-analysis. *J. Am. Heart Assoc.* **5**, 1–22 (2016).
20. Gershlick, A. H., Khan, J. N., Kelly, D. J., *et al.* Randomized trial of complete versus lesion-only revascularization in patients undergoing primary percutaneous coronary intervention for stemi and multivessel disease: The CvLPRIT trial. *J. Am. Coll. Cardiol.* **65**, 963–972 (2015).
21. Di Gioia, G., Sonck, J., Ferenc, M., *et al.* Clinical Outcomes Following Coronary Bifurcation PCI Techniques: A Systematic Review and Network Meta-Analysis Comprising 5,711 Patients. *JACC Cardiovasc. Interv.* **13**, 1432–1444 (2020).
22. Valgimigli, M., Bueno, H., Byrne, R. A., *et al.* 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS. *Eur. J. Cardio-thoracic Surg.* **53**, 34–78 (2018).

FIGURE LEGENDS

Table 1. Baseline characteristics of cases included in the study. SD: standard deviation. PCI: percutaneous coronary intervention, CABG: coronary artery bypass grafting, OOHCA: out of hospital cardiac arrest, NYHA: New York Heart Association, CCS: Canadian Cardiovascular Society

Table 2. Procedural characteristics of cases included in the study. ACS: acute coronary syndrome, IVUS: intravascular ultrasound, OCT: optical coherence tomography, LAD: left anterior descending, PCI: percutaneous coronary interventions, Cx: circumflex artery, RCA: right coronary artery, SD: standard deviation

Table 3. Unadjusted outcomes of cases included in the study. DCCV: DC cardioversion.

Figure 1. Multivariate-adjusted model for 30-day mortality in LMS-PCI cases 2016-2020

Figure 2. Multivariate-adjusted model for 12-month mortality in LMS-PCI cases 2016-2020

Supplementary Table S1. Missing values from variables in the data set