**Intravascular imaging and 12-month mortality after unprotected left main stem PCI: an analysis of 11,624 cases from British Cardiovascular Intervention Society database**

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**Abstract**

**Background:** Limited registry data supports the use of intravascular imaging during unprotected left main-stem PCI (uLMS-PCI) to improve outcomes. We used the BCIS national PCI database to explore temporal changes in the use of intravascular imaging for uLMS-PCI, defined the associates of imaging use, and correlate clinical outcomes including survival with imaging use. **Methods:** Data were analysed from 11,264 uLMS-PCI procedures performed in England and Wales between 2007 and 2014. Multivariate logistic regression was used to identify associates of imaging use. Propensity matching created 5,056 pairs of subjects with and without imaging, and logistic regression performed to quantify the association between imaging and outcomes. Multivariate logistic regression to identify the independent predictors of 12-month mortality was performed. **Results:** Imaging use increased from 30.2% in 2007 to 50.2% in 2014 (p<0.001 for trend). The factors associated with imaging use included stable angina presentation (OR 1.20, 95% confidence interval [1.147:1.246)], p<0.001), bifurcation LMS disease (OR 1.22 [1.14:1.30], p<0.001), previous PCI (OR 1.32 [1.20:1.44], p<0.001), and radial access (OR 1.266 [1.217:1.317], p<0.001). A lower rate of coronary complications, lower in-hospital MACE (OR 0.47 [0.37:0.59], p<0.001), and improved 30-day mortality (OR 0.54 [0.43:0.68], p<0.001) and 12-month mortality (OR 0.66 [0.57:0.77], p<0.001) were observed with imaging use compared to no imaging use. Greater mortality reductions were observed with higher operator LMS-PCI volume. In logistic regression modelling, imaging use was associated with improved 12-month survival. **Conclusions:** The observed lower mortality with use of intravascular imaging to guide uLMS-PCI justifies the undertaking of a large-scale randomised trial.

**Condensed abstract**

We used the BCIS national PCI database to explore use of intravascular imaging for uLMS-PCI. Intravascular imaging use increased from 30.2% in 2007 to 50.2% in 2014 (p<0.001 for trend). The factors associated with imaging use included stable angina presentation, bifurcation LMS disease, previous PCI, radial access, and trainee first operator. Imaging use was associated with a lower rate of coronary complications, lower in-hospital MACE (OR 0.47 [0.37:0.59], p<0.001), 30-day mortality (OR 0.54 [0.43:0.68], p<0.001) and 12-month mortality (OR 0.66 [0.57:0.77], p<0.001) when compared to no imaging use. In logistic regression modelling, imaging use was associated with improved 12-month survival.

**List of abbreviations**

BCIS - British Cardiovascular Intervention Society

CABG – coronary artery bypass surgery

FA - femoral access

IVUS - Intravascular ultrasound

LAD – left anterior descending

LMS - left main stem

MACCE - major adverse cardiac or cerebrovascular events

MI – myocardial infarction

NYHA – New York Heart Association

OCT - optical coherence tomography,

PCI - percutaneous coronary intervention

uLMS-PCI – unprotected left main stem percutaneous intervention

**Introduction**

Percutaneous coronary intervention (PCI) is increasingly considered as a revascularisation strategy in certain anatomical and patient subsets of unprotected left main stem (uLMS) disease. The European Society of Cardiology 2018 Guidelines on myocardial revascularization state that “PCI is an appropriate alternative to coronary artery bypass surgery (CABG) in uLMS disease of low-to-intermediate anatomical complexity”.(1) However, the role of intravascular imaging to guide uLMS-PCI is less clear. It is well recognised that sizing of the LMS is difficult to assess angiographically as a result of the lack of a proximal reference vessel.(2) Additionally, atherosclerosis at the LMS site frequently involves its distal bifurcation, with a high burden of fibrotic and calcific components, making PCI more technically challenging.(3,4) Therefore the role of intravascular imaging in guiding uLMS-PCI to improve outcomes is plausible and attractive.

In the Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery (SYNTAX) trial, intravascular ultrasound (IVUS) was not mandated as part of the study protocol and was only used in 4.8% of the PCI arm.(5,6) Despite this, the trial demonstrated impressive outcomes versus CABG for low and intermediate SYNTAX tertile groups. In an effort to further improve the outcomes of uLMS-PCI, contemporary randomised trials of uLMS-PCI vs. CABG have utilised as contemporary interventional strategy as possible including IVUS. In the Everolimus-Eluting Stents or Bypass Surgery for Left Main Coronary Artery Disease (EXCEL) trial, IVUS use was strongly recommended and in actuality was used in 77.2% of the PCI arm.(7) In the Nordic–Baltic–British left main revascularisation study (NOBLE), IVUS was used to evaluate the post-procedure result in 74% of the PCI arm.(8) To date the outcomes by IVUS use have not been reported separately for either trial.

# There is limited randomised trials of intravascular ultrasound (IVUS) in guiding uLMS-PCI with much of the evidence derived from modest sized observational registries. Therefore, the aim of the current study was to add further evidence as to the role of intravascular imaging guidance of uLMS-PCI, by deriving data from a large national database. To do this we used the United Kingdom National PCI Audit to explore temporal changes in the use of intravascular imaging for uLMS-PCI, defined the associates of imaging use, and correlated clinical outcomes including 12-month survival with imaging use.

**Methods**

*Study design and participants*

We analysed data from all patients undergoing uLMS-PCI in England and Wales between January 1st 2007 and December 31st 2014. The study patient flow is illustrated in Supplementary Figure 1. Participants with PCI to a protected LMS were excluded from the analysis. Additionally, patients with cardiogenic shock, or missing information on target vessel, or imaging status were also excluded.

*Study setting and sources of data*

Data on PCI practice were obtained from the BCIS National PCI Audit dataset which records 113 clinical, procedural and outcomes variables for every PCI performed in the UK, and thus approximately 100,000 new records are currently recorded each year. Entry of all PCI procedures by UK interventional operators is mandated as part of their professional revalidation. The accuracy of and quality of the BCIS dataset has previously been ascertained.(9) The patients in the database are tracked by linkage with life status information held by the Office of National Statistics (ONS) using each patient’s unique NHS number. However, although all 4 countries within the United Kingdom enter PCI data, ONS mortality tracking is only available for England and Wales.

*Study definitions*

The BCIS National PCI Audit records intravascular imaging as IVUS or swept laser imaging (to include optical coherence tomography (OCT) and optical frequency domain imaging (OFDI). Patients were categorised into either imaging-guided or angiography-guided uLMS-PCI. Study definitions were used as in the BCIS National PCI Audit (available at https://www.bcis.org.uk/resources/bcis-ccad-database-resources/datasets-history/). Pre- or post-PCI disease severity was defined as vessels with a stenosis ≥70% in the case of the LAD, circumflex or right coronary arteries, or ≥50% in the case of the left main artery. Chronic renal failure was defined as chronic dialysis, history of renal transplant or a creatinine >200umol/l. In-hospital major bleeding was defined as a combination of gastrointestinal bleeding, intracerebral bleeding, retroperitoneal haematoma, blood or platelet transfusion, access site haemorrhage, and/or an arterial access site complication requiring surgery. In-hospital major adverse cardiac or cerebrovascular events (MACCE) were defined as a combination of death, stroke, or myocardial infarction (or re-infarction, depending on indication) after PCI.

*Data analyses*

Trends for the use of imaging over time and type of imaging were constructed and significance was examined using linear regression. We examined the baseline characteristics of participants by intravascular imaging status. We tested for associations between each categorical variable and imaging using a Chi-squared test, and continuous variables using one-way analysis of variance. Independent predictors of the use of intravascular imaging were evaluated using a multivariate logistic regression model to generate odds ratios, 95% confidence intervals and corresponding p-values. To select predictors to enter into the final multivariate model we used forward stepwise variable selection on the data and an inclusion criterion of p<0.1. To correct for missing values, we imputed missing data on baseline covariates using multiple imputations with chained equations to adjust for missing data (Supplementary Table 1). Covariates included in the model were age, gender, clinical syndrome, NYHA class, previous MI, hypertension, diabetes, ejection fraction <30%, peripheral vascular disease, previous stroke, history of renal disease, Q wave on ECG, previous PCI, year of PCI, baseline disease severity and pattern, operator status, rotational atherectomy use, ad-hoc PCI, and access site.

For clinical outcomes we initially calculated the crude rates by imaging status. Individual logistic regressions were undertaken on the imputed data set for each of the outcome events according to the imaging status to quantify the independent association between imaging and outcomes. To adjust for baseline characteristics that might influence outcomes, we used a propensity matching technique to correct for those imbalances. We first estimated the probability a patient was part of the no imaging group versus being part of the imaging group (the propensity score). The probability was estimated using logistic regression with Imaging group yes/no as the dependent variable and a set of specified baseline variables. The covariates included in the model were age, sex, clinical presentation, NYHA class, previous MI, previous PCI, diabetes, hypertension, peripheral vascular disease, previous stroke, renal impairment, Q wave on ECG, glycoprotein inhibitor use and left ventricular support use. Multiple imputation was used to generate 10 complete datasets, 10 distinct propensity scores from a logistic regression for all patients and we considered a patient’s propensity score the average over all 10 values. We then ran a 1:1 propensity matching creating pairs of patients that had similar propensity score. Propensity scores had to be within a range defined as 1/4 the propensity-score standard deviation and we excluded the no-imaging patients without a matching imaging patient. Out of the 6208 patients with imaging, 5056 pairs of subjects were created to match the original 5056 patients without imaging. The matched cohorts are presenting in Supplementary Table 2. A sensitivity analysis examining the role of imaging in several sub-groups including operator volume, left main complexity and clinical presentation was also performed. Finally, we performed an analysis of the predictors of 12-month mortality using a multivariate logistic regression model to generate odds ratios, 95% confidence intervals and corresponding p-values.

**Results**

*Temporal changes in imaging use for unprotected left main PCI between 2007 and 2014*

The study flow is illustrated in Supplementary Figure 1 with 11,264 patients who underwent PCI to the left main stem between 2007 and 2014 included in the analysis. Crude numbers of LMS-PCI increased significantly during the study period, as did LMS-PCI activity of as a percentage of the total PCI (increasing from 2.0% to 4.1%, p<0.001 for trend, Supplementary Figure 2). Whilst the use of imaging for protected LMS-PCI did not change significantly over the study period, use of imaging for unprotected LMS-PCI increased from 30.2% to 50.2% of cases (Figure 1 left panel, p<0.001 for trend). Temporal changes in Intravascular imaging by device type are presented in Figure 1 (right panel) illustrating the emergence of OCT in later study years.

*Baseline demographics, and procedural data by imaging status for unprotected left main PCI between 2007 and 2014*

In total, 11,264 uLMS-PCI procedures were performed between 2007 and 2014. Of these, 5,056 procedures were guided by intravascular imaging. The baseline demographics by intravascular imaging status are presented in Table 1. Patients in whom imaging was used were younger, more likely to be male, have a history of a previous PCI, and present with stable angina. Conversely, patients without imaging use had a greater degree of comorbidity including hypertension, diabetes mellitus, previous MI, previous stroke, low EF, peripheral vascular disease, and chronic renal disease. Baseline disease burden was greater in patients in whom intravascular imaging was not used (2.13±1.00 vessels vs. 1.90±0.91 vessels, p<0.001).

Procedural data by imaging group are presented in Table 2. During the uLMS-PCI procedure, radial access and a trainee first operator were more likely in the group in which imaging was used, whilst circulatory support use was less frequent. LMS only as the target vessel was more likely in the angiography-guided group, whilst LMS/LAD, and LMS/LAD/circumflex as target vessels were significantly more likely in the imaging-guided group. The largest stent diameter (4.3±0.68mm vs. 3.9±0.67mm, p<0.001) was greater in the group in which imaging was used, as was the longest stent length (24.1±10.2mm vs. 23.3±9.4mm, p<0.001). When analysed by quartiles of uLMS-PCI operator volume, imaging use increased from Quartile 1 to Quartile 3 and a reduced in Quartile 4 (Figure 2).

*Independent associates of imaging during unprotected LMS-PCI from 2007 to 2014*

The factors independently associated with an increased likelihood of imaging use are presented in Table 3 and include radial access (OR 1.266, [95% confidence intervals 1.22:1.32], p<0.001), bifurcation LMS disease (OR 1.22 [1.14:1.30], p<0.001), stable angina presentation (OR 1.20, [1.15:1.25)], p<0.001), and trainee first operator (OR 1.14 [1.09:1.19], p<0.001). Increasing complexity of baseline disease and an ejection fraction of <30% were associated with a lower likelihood of imaging use.

*Clinical outcomes by imaging for unprotected LMS-PCI from 2007 to 2014*

Procedural success was higher in the imaging-guided group with a greater number of successful lesions (2.01±1.06 vs. 1.97±1.04, p=0.007, Table 4) and a lower post-procedural angiographic residual disease burden than the angiography-guided group (0.38±0.75 vs. 0.59±0.85 vessels, p<0.001). A lower rate of slow flow was observed in the imaging group (0.7 vs. 1.4%, p=0.002) with the occurrence of any immediate coronary complications also lower (7.0% vs. 8.7%, p=0.003). In unadjusted analysis, several clinical adverse outcomes including in-hospital major bleeding, in-hospital MACCE and mortality after discharge were observed less frequently in the imaging-guided compared to the angiography-guided group. This was also the case after using propensity scoring to adjust for baseline imbalances between groups, with slow flow (OR 0.51, [95% confidence intervals 0.33:0.77], p=0.001), coronary dissection (OR 0.82, [95% confidence intervals 0.69:0.98], p=0.028), any coronary complication (OR 0.78, [95% confidence intervals 0.33:0.77], p=0.001), in-hospital death (OR 0.39 [0.29:0.51], p<0.001), in-hospital MACCE (OR 0.47 [0.38:0.59], p<0.001, 30-day mortality (OR 0.54, [0.43:0.68], p<0.0010 and 12-month mortality (OR 0.66, [0.57:0.77], p<0.001) observed less frequently in the imaging-guided group (Table 5). Figure 3 illustrates the Kaplan Meier plots for mortality by imaging status to 12-months demonstrating the observation of a temporal reduction in mortality when imaging was used during uLMS-PCI. An annualised survival analysis demonstrated that the mortality reduction associated with imaging use persisted throughout the study period (Supplementary Figure 3).

In a multi-variable analysis of the predictors of 12-month mortality after unprotected LMS-PCI, use of intravascular imaging was associated with lower mortality (OR 0.77 [0.69:0.86], p<0.001). In sensitivity analyses, there appeared to be a significant subgroup interaction with respect to operator volume and to anatomical complexity, with greater mortality benefit with imaging observed with higher operator volumes and procedures that involved both the left main (p-value for interaction=0.035) and left anterior descending arteries (p-value for interaction=0.048, Figure 4).

Figure 5 illustrates the limitation of using angiography-only in guiding LMS-PCI, with poor sensitivity for confirming complete stent apposition

**Discussion**

The findings of the current study can be summarised as follows: 1) Intravascular imaging rates for uLMS-PCI increased significantly over the study period, with ~50% of procedures utilising imaging in the most contemporary study year; 2) the predictors of intravascular imaging use included stable angina presentation, radial access and bifurcation disease: 3) intravascular imaging use was observed to be associated with a greater length of stent and a larger stent diameter; 4) intravascular imaging use was observed to be associated with fewer acute procedural complications and improved short and medium-term survival.

The observed increased use of PCI to treat uLMS in England and Wales likely reflects the increased enthusiasm of operators and patients to use a percutaneous strategy rather than CABG. In the current study IVUS dominates as the technology used, although OCT use increased in later study years. Although the left main can be technically challenging to image with OCT, several on-going uLMS-PCI trials are using OCT in follow-up to assess stent healing.(11) However, the observation that even in the most recent study year, imaging was used in only half of uLMS-PCI procedures is worthy of further comment. The most recent United Kingdom National PCI audit data for 2017-18 shows that the use of imaging seems to have plateaued over recent years.(12) This modest uptake of intracoronary imaging may be due to several factors. Firstly, many operators performing uLMS-PCI may not be confident in the performance and accurate interpretation of images. Secondly the added procedural time of intravascular imaging might lead to operators feeling pressured to complete the case and optimize lab throughput. Thirdly, depending on the healthcare system, there may be a financial dis-incentive to perform imaging. Finally, these factors may be further compounded by the international PCI guidelines which do not robustly recommend such additional imaging, perhaps reflecting a paucity of positive randomised trial data in its favour. For example, the European Society 2018 Guidelines on myocardial revascularization state that IVUS should be “considered to optimize treatment of unprotected left main lesions” with a Class IIa recommendation and a B Level of Evidence.(1) The American College of Cardiology Foundation/ Society for Cardiovascular Angiography and Interventions Expert Consensus Document on Cardiac Catheterization Laboratory Standards Update similarly provide modest support.(13) In contrast, a recent consensus document from the European Bifurcation Club recommended routine use of intravascular imaging to guide LMS intervention.(14) Whilst the observation that a trainee first operator was independently associated with an increased likelihood of imaging use may reflect less complex anatomy being undertaken by a trainee, it may also be explained by a trainee being more likely to be the primary operator in an on-site surgery PCI centre. Indeed, the association between imaging use and on-site surgery might support this hypothesis.

With regard to supportive evidence for intracoronary imaging in uLMS-PCI, there is a lack of randomised trials so that the majority of the data are derived from modestly sized observational registries. These data overall provide circumstantial evidence of benefit for intracoronary imaging. In the largest registry to date, 2,468 patients who underwent uLMS-PCI between 2005 and 2014 in the Swedish Coronary Angiography and Angioplasty Registry (SCAAR) were studied.(15) In the 621 in whom IVUS was used, the observed all-cause mortality was significantly lower than in the non-imaging cohort (hazard ratio, 0.62; 95% confidence interval, 0.47–0.82). In the MAIN-COMPARE (revascularization for unprotected left MAIN coronary artery stenosis: COMparison of Percutaneous coronary Angioplasty versus surgical REvascularization) registry of patients undergoing uLMS-PCI, IVUS use in 145 matched pairs of patients treated with a drug-eluting stent was associated with a significantly lower 3-year mortality compared to patients where IVUS was not used (4.7% versus 16.0%, p=0.048).(16) A pooled analysis of 4 Spanish registries examined the outcomes of 1,670 uLMS-PCI patients. By means of matching, 505 patient pairs were constructed and survival free of cardiac death, myocardial infarction, and target lesion revascularization at 3 years was 88.7% in the IVUS group and 83.6% in the no-IVUS group (p=0.04).(17) Several other modest sized registries have similarly observed a reduction in mortality and/or MACE in patients in whom intravascular imaging was used to guide uLMS-PCI compared to angiography-guided PCI.(18,19) Two small randomised trials have demonstrated similar improvements in outcomes with intravascular imaging. Tan et al randomised 123 patients over 70 years of age to IVUS or no IVUS use. IVUS use was associated with a lower MACE at 2 years (12.8% versus 27.3% *p*=0.049).(20) Liu et al randomised 336 consecutive patients into IVUS-guided group (n=167) and control groups (n=169). After a 1-year follow-up, the occurrence of composite MACE in the IVUS-guided group was significantly lower than that in the control group (13.2% vs. 21.9%, p=0.031).(21) Despite these 2 randomised trials supporting use of imaging, their small size increases the possibility of a Type 1 (statistical) error - a concern that larger studies would address.

Exactly how imaging was used to guide uLMS-PCI (i.e. pre- or post-PCI or both) in UK practice is not recorded in the BCIS database. Indeed, these procedural details are inconsistently reported in the literature. In the only other publication from a national registry of imaging to guide uLMS-PCI, Andell et al using data derived from SCAAR also did not report exactly how the imaging was utilised.(15) This likely reflects the difficulty national databases encounter in balancing the acquisition of huge volumes of data on all PCI procedures against the practicalities of overly onerous data entry. However, best practice in the use of imaging to guide uLMS-PCI, is for it to be used not only pre-PCI to accurately measure stent size, length and appropriate landing zones, but also post-PCI to ensure optimal stent expansion and malapposition.(14).

Although we attempted to correct for baseline differences between the two cohorts by using propensity matching, it remains possible that unmeasured confounders have biased the results. The BCIS registry does record data on several comorbidities including hypertension, diabetes mellitus, low ejection fraction, peripheral vascular disease, cerebrovascular disease, renal disease, previous myocardial infarction and valvular disease. Therefore, although these factors can be adjusted for in the statistical modelling, other unmeasured confounders such as comorbidity that is not captured by the database could influence the results. The lack of an association after matching for adverse outcomes that one would not expect to be affected by imaging - such as acute kidney injury or major bleeding - is reassuring that the patients are reasonably well matched. The observation of a 34% lower 12-month mortality associated with imaging-guided uLMS-PCI in the current study is similar to the mortality reduction observed in meta-analyses of the published and un-published registries and one of the randomised trials.(22,23) These analyses demonstrated that compared with angiography-guided PCI, IVUS-guided PCI was associated with significantly lower risks of all-cause death (risk ratio 0.60, 95% confidence interval 0.47–0.75, p<0.001) and cardiac death (risk ratio 0.47, 95% confidence interval 0.33–0.66, p<0.001). Although confounding remains a possibility in the current study (as in all similar registry analyses), the consistency of the observed mortality reduction with imaging use in the differing the registries and (albeit small) randomised trials is reassuring. However, despite our best attempts to mitigate the effects of confounding, the only true way to robustly examine whether imaging guidance for uLMS-PCI reduces mortality is a large-scale randomised trial.

There may be several plausible explanations underpinning the potentially lower mortality when uLMS-PCI is guided by intravascular imaging. Fewer immediate procedural complications were observed with use of imaging to guide PCI. After adjustment, slow flow, coronary dissection, and any coronary complication were lower when intravascular imaging was used, which might be explained by optimal vessel sizing and stent placement facilitated by imaging. Although previous studies of IVUS-guidance for uLMS-PCI have not reported acute procedural complications, their occurrence has been correlated with reduced 12-month survival in non-LMS studies.(24,25) Better lesion coverage, optimal stent sizing, improved stent expansion and optimisation, early identification of local complications such as edge dissection and more complete revascularisation facilitated by intravascular imaging are also likely to reduce adverse outcomes during follow-up. Previous studies have demonstrated that angiographic assessment of the left main artery by angiography alone is difficult. Specifically, not only is the angiographic assessment of lesion severity most variable in the left main artery, but sizing is more difficult than in any other coronary vessel.(14,26) In the current study intravascular imaging led to a greater length and size of stent implanted in comparison to angiography guided PCI, an observation seen in several other studies.(17,18,20) Although stent thrombosis and TLR rates are not available in the current study, previous studies have demonstrated very significant reductions in the frequency of these end points with IVUS-guided uLMS-PCI, findings that have been consistently seen in all studies that have employed intracoronary imaging in any PCI using stents (bare metal and drug-eluting). Thus, in the meta-analysis performed by Ye et al, IVUS-guided uLMS-PCI was associated with lower rates of target lesion revascularization (risk ratio 0.43, 95% confidence interval 0.25–0.73, p = 0.002), and stent thrombosis (risk ratio 0.28, 95% confidence interval 0.12–0.67, p=0.004) compared to angiography-guided uLMS-PCI.(22) In a second meta-analysis, stent thrombosis by 52% lower in the cohort with IVUS use.(23)

The finding that imaging use increased through quartile 1 to 3 of operator volume but conversely a drop in usage in quartile 4 contrasts with previous data and might be explained by a perceived lack of need in the most experienced operators.(27) However, the sensitivity analysis demonstrates an interaction between volume and outcomes, with the greatest reductions in 12-months mortality observed in the highest operator quartile. The additional observation in the sensitivity analysis of a additional gain with imaging when the left main PCI involves the LAD compared to the left main only, coupled with previous data correlating operator PCI volume and procedural complexity implies that higher volume operators take on more complex left main anatomy and thus have more rather than less to gain from intravascular imaging.(28) Indeed, LMS lesion complexity clearly correlates with outcomes with the EXCEL trial (Evaluation of XIENCE Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) demonstrating significantly greater death, myocardial infarction, or stroke at 3 years with a 2-stent versus a 1-stent strategy. These data therefore support the use if intravascular imaging regardless of operator volume and experience.(29)

The major strengths of this study are several fold. Only one other study of national uLMS-PCI imaging practice has been published and only 621 procedures were reported. Therefore, this is much larger than any other single study of uLMS-PCI and more importantly than any other national database analysis.(15) Secondly, the current series reports procedures from more contemporary study years in comparison to many of the previous studies which reported outcomes with a large proportion of first-generation DES or bare metal stents. As a result of the more contemporary study period, second generation stents were used in the majority of cases in the current study. It is an important finding that the observed reduction in mortality associated with imaging is maintained following uLMS-PCI, as in theory it might be ameliorated by later iterations of stents with undoubtedly improved healing in comparison to first generation stents or bare-metal stents. Thirdly, the longitudinal nature of this study provides for the first time that the observed reduction of mortality with imaging use is maintained over time despite iterations in procedural equipment and interventional techniques. Finally, this is the first study of imaging and uLMS-PCI to have sufficient statistical power to perform a robust sensitivity analysis. This allowed for the first time and association between operator volume and improved outcomes with imaging to be observed. This is an important finding and reiterates the potential benefit of imaging regardless of operator experience.

In considering the limitations of the present study aside from unmeasured confounders as discussed above. Although an annualised analysis of mortality by imaging group demonstrated a consistent reduction associated with imaging use, the observational nature of the data means that it is impossible to rule out that the improved outcome associated with imaging is not confounded by increased levels of experience, skills, and improvements in interventional equipment. Additionally, the BCIS database does not capture details of anatomical data such as the location of disease with the LMS, complexity of lesions such as calcification or the presence or type of distal LMS bifurcation disease. Therefore, we cannot provide detailed data on the relationship to the pattern of disease and imaging. In an attempt to partly address this limitation, we categorised patients as a surrogate into LMS only and several sub-categories of LMS with other vessels treated. Similarly, whilst there are robust data regarding the type and number of stents used, there are no data provided on the technical approach used to treat the LMS disease. Finally, whilst the purpose of the current study was to examine on a national basis the relationship between imaging use per se and mortality, as the BCIS database does not capture IVUS data we cannot provide details of minimal luminal and stent area and correlate these with outcomes.

**Conclusions**

Although the uptake of intravascular imaging for unprotected LMS-PCI increased each year, only 50% of cases in the most recent years utilised this technology. The observation in this large cohort of procedures that use of intravascular imaging was associated with fewer acute procedural complications, and better short and long-term survival supports the need for large multi-centre randomised trials.

**References**

1. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet JP, Falk V, Head SJ, Jüni P, Kastrati A, Koller A, Kristensen SD, Niebauer J, Richter DJ, Seferovic PM, Sibbing D, Stefanini GG, Windecker S, Yadav R, Zembala MO; ESC Scientific Document Group. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J. 2019;40(2):87-165.
2. Lefèvre T, Girasis C, Lassen JF. Differences between the left main and other bifurcations. EuroIntervention. 2015;11 Suppl V:V106-10. doi: 10.4244/EIJV11SVA24.
3. Wykrzykowska JJ, Mintz GS, Garcia-Garcia HM, Maehara A, Fahy M, Xu K, Inguez A, Fajadet J, Lansky A, Templin B, Zhang Z, de Bruyne B, Weisz G, Serruys PW, Stone GW. Longitudinal distribution of plaque burden and necrotic core-rich plaques in nonculprit lesions of patients presenting with acute coronary syndromes. JACC Cardiovasc Imaging. 2012;5(3 Suppl):S10-8.
4. Mercado N, Moe TG, Pieper M, House JA, Dolla WJ, Seifert L, Stolker JM, Lindsey JB, Kennedy KF, Marso SP. Tissue characterisation of atherosclerotic plaque in the left main: an in vivo intravascular ultrasound radiofrequency data analysis. EuroIntervention. 2011;7(3):347-52.
5. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, Ståhle E, Feldman TE, van den Brand M, Bass EJ, Van Dyck N, Leadley K, Dawkins KD, Mohr FW; SYNTAX Investigators. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med. 2009;360(10):961-72.
6. Morice MC, Serruys PW, Kappetein AP, Feldman TE, Ståhle E, Colombo A, Mack MJ, Holmes DR, Torracca L, van Es GA, Leadley K, Dawkins KD, Mohr F. Outcomes in patients with de novo left main disease treated with either percutaneous coronary intervention using paclitaxel-eluting stents or coronary artery bypass graft treatment in the Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery (SYNTAX) trial. Circulation. 2010;121(24):2645-53.
7. Stone GW, Sabik JF, Serruys PW, Simonton CA, Généreux P, Puskas J, Kandzari DE, Morice MC, Lembo N, Brown WM 3rd, Taggart DP, Banning A, Merkely B, Horkay F, Boonstra PW, van Boven AJ, Ungi I, Bogáts G, Mansour S, Noiseux N, Sabaté M, Pomar J, Hickey M, Gershlick A, Buszman P, Bochenek A, Schampaert E, Pagé P, Dressler O, Kosmidou I, Mehran R, Pocock SJ, Kappetein AP; EXCEL Trial Investigators. Everolimus-Eluting Stents or Bypass Surgery for Left Main Coronary Artery Disease. N Engl J Med. 2016;375(23):2223-2235.
8. Mäkikallio T, Holm NR, Lindsay M, Spence MS, Erglis A, Menown IB, Trovik T, Eskola M, Romppanen H, Kellerth T, Ravkilde J, Jensen LO, Kalinauskas G, Linder RB, Pentikainen M, Hervold A, Banning A, Zaman A, Cotton J, Eriksen E, Margus S, Sørensen HT, Nielsen PH, Niemelä M, Kervinen K, Lassen JF, Maeng M, Oldroyd K, Berg G, Walsh SJ, Hanratty CG, Kumsars I, Stradins P, Steigen TK, Fröbert O, Graham AN, Endresen PC, Corbascio M, Kajander O, Trivedi U, Hartikainen J, Anttila V, Hildick-Smith D, Thuesen L, Christiansen EH; NOBLE study investigators. 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. 2016;388(10061):2743-2752.
9. Ludman PF; British Cardiovascular Intervention Society. British Cardiovascular Intervention Society Registry for audit and quality assessment of percutaneous coronary interventions in the United Kingdom. Heart. 2011;97:1293-7.
10. Elze MC, Gregson J, Baber U, Williamson E, Sartori S, Mehran R, Nichols M, Stone GW, Pocock SJ. Comparison of Propensity Score Methods and Covariate Adjustment: Evaluation in 4 Cardiovascular Studies. J Am Coll Cardiol. 2017;69(3):345-357.
11. Lemmert ME, Oldroyd K, Barragan P, Lesiak M, Byrne RA, Merkulov E, Daemen J, Onuma Y, Witberg K, van Geuns RJ. Reduced duration of dual antiplatelet therapy using an improved drug-eluting stent for percutaneous coronary intervention of the left main artery in a real-world, all-comer population: Rationale and study design of the prospective randomized multicenter IDEAL-LM trial. Am Heart J. 2017;187:104-111.
12. <https://www.bcis.org.uk/education/bcis-audit-report-2017-18/> (last accessed February 22nd, 2019)
13. Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, Chambers CE, Ellis SG, Guyton RA, Hollenberg SM, Khot UN, Lange RA, Mauri L, Mehran R, Moussa ID, Mukherjee D, Nallamothu BK, Ting HH; American College of Cardiology Foundation; American Heart Association Task Force on Practice Guidelines; Society for Cardiovascular Angiography and Interventions. 2011ACCF/AHA/ SCAI Guideline for Percutaneous Coronary Intervention: execu- tive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. Catheter Cardiovasc Interv 2012; 79: 453-95.
14. Mintz GS, Lefèvre T, Lassen JF, Testa L, Pan M, Singh J, Stankovic G, Banning AP. Intravascular ultrasound in the evaluation and treatment of left main coronary artery disease: a consensus statement from the European Bifurcation Club. EuroIntervention. 2018 Jul 20;14(4):e467-e474. doi: 10.4244/EIJ-D-18-00194.
15. Andell P, Karlsson S, Mohammad MA, Götberg M, James S, Jensen J, Fröbert O, Angerås O, Nilsson J, Omerovic E, Lagerqvist B, Persson J, Koul S, Erlinge D. Intravascular Ultrasound Guidance Is Associated With Better Outcome in Patients Undergoing Unprotected Left Main Coronary Artery Stenting Compared With Angiography Guidance Alone. Circ Cardiovasc Interv. 2017;10(5). pii: e004813.
16. Park DW, Seung KB, Kim YH, Lee JY, Kim WJ, Kang SJ, Lee SW, Lee CW, Park SW, Yun SC, Gwon HC, Jeong MH, Jang YS, Kim HS, Kim PJ, Seong IW, Park HS, Ahn T, Chae IH, Tahk SJ, Chung WS, Park SJ. Long-term safety and efficacy of stenting versus coronary artery bypass grafting for unprotected left main coronary artery disease: 5-year results from the MAIN-COMPARE (Revascularization for Unprotected Left Main Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty Versus Surgical Revascularization) registry. J Am Coll Cardiol. 2010;56(2):117-24.
17. de la Torre Hernandez JM, Baz Alonso JA, Gómez Hospital JA, Alfonso Manterola F, Garcia Camarero T, Gimeno de Carlos F, Roura Ferrer G, Recalde AS, Martínez-Luengas IL, Gomez Lara J, Hernandez Hernandez F, Pérez-Vizcayno MJ, Cequier Fillat A, Perez de Prado A, Gonzalez-Trevilla AA, Jimenez Navarro MF, Mauri Ferre J, Fernandez Diaz JA, Pinar Bermudez E, Zueco Gil J; IVUS-TRONCO-ICP Spanish study. Clinical impact of intravascular ultrasound guidance in drug-eluting stent implantation for unprotected left main coronary disease: pooled analysis at the patient-level of 4 registries. JACC Cardiovasc Interv. 2014 Mar;7(3):244-54. doi: 10.1016/j.jcin.2013.09.014.
18. Gao XF, Kan J, Zhang YJ, Zhang JJ, Tian NL, Ye F, Ge Z, Xiao PX, Chen F, Mintz G, Chen SL. Comparison of one-year clinical outcomes between intravascular ultrasound-guided versus angiography-guided implantation of drug-eluting stents for left main lesions: a single-center analysis of a 1,016-patient cohort. Patient Prefer Adherence. 2014;8:1299-309.
19. Tian J, Guan C, Wang W, Zhang K, Chen J, Wu Y, Yan H, Zhao Y, Qiao S, Yang Y, Mintz GS, Xu B, Tang Y. Intravascular Ultrasound Guidance Improves the Long-term Prognosis in Patients with Unprotected Left: 10.1038/s41598-017-02649-5.
20. Tan Q, Wang Q, Liu D, Zhang S, Zhang Y, Li Y. Intravascular ultrasound-guided unprotected left main coronary artery stenting in the elderly. Saudi Med J. 2015;36(5):549-53.
21. Liu XM, Yang ZM, Liu XK, Zhang Q, Liu CQ, Han QL, Sun JH. Intravascular ultrasound-guided drug-eluting stent implantation for patients with unprotected left main coronary artery lesions: A single-center randomized trial. Anatol J Cardiol. 2019;21(2):83-90.
22. Ye Y, Yang M, Zhang S, Zeng Y. Percutaneous coronary intervention in left main coronary artery disease with or without intravascular ultrasound: A meta-analysis. PLoS One. 2017;12(6):e0179756.
23. Wang Y, Mintz GS, Gu Z, Qi Y, Wang Y, Liu M, Wu X. Meta-analysis and systematic review of intravascular ultrasound versus angiography-guided drug eluting stent implantation in left main coronary disease in 4592 patients. BMC Cardiovasc Disord. 2018;18(1):115.
24. Kim DW, Her SH, Park MW, Cho JS, Kim TS, Kang H, Sim DS, Hong YJ, Kim JH, Ahn Y, Chang K, Chung WS, Seung KB, Jeong MH, Rho TH. Impact of Postprocedural TIMI Flow on Long-Term Clinical Outcomes in Patients with Acute Myocardial Infarction. Int Heart J. 2017;58(5):674-685.
25. Cheng CI, Wu CJ, Hsieh YK, Chen YH, Chen CJ, Chen SM, Yang CH, Hung WC, Yip HK, Chen MC, Fu M, Fang CY. Percutaneous coronary intervention for iatrogenic left main coronary artery dissection. Int J Cardiol. 2008;126(2):177-82.
26. Fisher LD, Judkins MP, Lesperance J, Cameron A, Swaye P, Ryan T, Maynard C, Bourassa M, Kennedy JW, Gosselin A, Kemp H, Faxon D, Wexler L, Davis KB. Reproducibility of coronary arteriographic reading in the coronary artery surgery study (CASS). Cathet Cardiovasc Diagn. 1982;8(6):565-75.
27. Xu B, Redfors B, Yang Y, et al. Impact of Operator Experience and Volume on Outcomes After Left Main Coronary Artery Percutaneous Coronary Intervention. JACC Cardiovasc Interv. 2016;9:2086-2093.
28. Hulme W, Sperrin M, Kinnaird T, et al. Operator volume is not associated with mortality following percutaneous coronary intervention: insights from the British Cardiovascular Intervention Society registry. Eur Heart J. 2018;39:1623-1634.
29. Kandzari DE, Gershlick AH, Serruys PW, et al. Outcomes Among Patients Undergoing Distal Left Main Percutaneous Coronary Intervention. Circ Cardiovasc Interv. 2018;11(10):e007007.

**Figure Legends**

**Figure 1: Trends in imaging for uLMS PCI in England and Wales 2007-2014.** Left panel - Percentage of intravascular imaging use during unprotected LMS-PCI (p-value<0.001 for trend comparison); Right panel - Temporal change in intravascular ultrasound (IVUS) vs. optical coherence tomography (OCT) use during uLMS-PCI

**Figure 2: Operator volume and intravascular imaging use.** Percentage of use during uLMS-PCI in England and Wales 2007-2014 presented by quartiles of operator uLMS-PCI volume indicating an increase in imaging use from Q1 to Q3 and a drop in use in Q4.

**Figure 3: Survival by intravascular imaging use after unprotected LMS-PCI in England and Wales 2007-2014.** Kaplan-Meier curves of 12-month mortality categorised by intravascular imaging use or not.

**Figure 4:** **Sub-group analysis of 12-month mortality by imaging use.** Forest plot of 12-month survival by imaging use in study sub-groups of operator volume, clinical presentation, ejection fraction and left main anatomy.

**Figure 5: Optical coherence tomography during LMS-PCI.** Panel A and D: Pre-PCI angiography and OCT indicating severe distal LMS disease and a minimal luminal diameter of 3.6mm2; Panel B and E: After post-dilation with a 4.0mm balloon, although angiography demonstrates an apparently good result, OCT demonstrates significant stent malapposition (white arrows); Panel C and F: After post-dilation with a 4.5mm balloon, although the angiogram appearances are unchanged, OCT confirms complete stent apposition (white arrows).