**The impact of diabetes on the prognostic value of left ventricular function following percutaneous coronary intervention: Insights from the British Cardiovascular Intervention Society.  
Short running title:** Prognostic interplay of LV function and diabetes status on patients undergoing PCI

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**Abstract**

**Objectives**

To study the relationship between Diabetes Mellitus (DM) and left ventricular (LV) function on outcomes following percutaneous coronary intervention (PCI).

**Background**

DM is a growing public health challenge worldwide and a significant risk factor for cardiovascular disease and heart failure.

**Methods**

All PCI procedures performed between 2006 and 2013 with LV function and diabetic status recorded in the BCIS-NICOR database were included. Demographic, procedural and clinical outcomes data were collected. Multivariable logistic regression was used to provide adjusted estimates of clinical outcome by LV function and DM, including DM sub-type.

**Results**

Of 260,726 patients, DM was present in 52,160 (20%); moderate LV systolic dysfunction (LVSD) was present in 51,266 (20%) and severe LVSD in 18,148 (7%). Worsening LVSD in diabetic patients was associated with poorer prognosis following PCI; moderate LVSD odds ratio (OR) 2.03 (95%CI 1.72-2.38) and severe LVSD OR 4.17 (95% CI 3.52-4.93). There was a higher crude and adjusted mortality rate for patients with DM across all grades of LVSD. However, the relative effect of DM appeared attenuated in the severe LVSD group compared with moderate or good LV function, particularly evident in patients with insulin requiring DM (good LV OR 2.09 (95% CI 1.66-2.65); moderate LVSD OR 1.56 (95% CI 1.26-1.93), poor LV OR 1.40 (95% CI 1.13-1.74).

**Conclusions**

Diabetes mellitus was associated with increased 30-day mortality for all grades of LV function. The prognostic impact of DM was strongest in patients with normal LV function and less evident in patients with severe LV systolic dysfunction.

**Keywords**

Coronary heart disease; Percutaneous coronary intervention; Diabetes mellitus; Left ventricular systolic dysfunction, British Cardiovascular Intervention Society, National Institute of Cardiovascular Outcomes.

**Word Count:** 2897

**Introduction**

Diabetes mellitus (DM) and associated vascular complications, present a major challenge to public health. The current worldwide DM prevalence of >400 million, is predicted to increase by over 50% to 2040 (1-3). Patients with DM and established atherothrombotic disease with pre-existing heart failure are at particularly high risk of adverse outcomes (4).

There has been an increase in the proportion of patients with established DM undergoing percutaneous coronary intervention (PCI) (5). Left ventricular systolic dysfunction (LVSD) is known to adversely impact early clinical outcome following PCI for all indications (6). Although the importance of diabetes in the development of LVSD (and subsequent heart failure) is recognised, the interplay between these factors in patients undergoing PCI is less well established.

The BCIS database includes virtually all PCI performed in the UK NHS and as such has the scale to estimate the influence of important factors on outcomes, including within subgroups. Our aim was to analyse outcomes for patients defined by their diabetes status (present or absent, and by treatment of diabetes) within different grades of LV function following PCI. We have focussed the analysis on early outcomes at 30-days.

**Methods**

We conducted a retrospective cohort study of all patients in England and Wales who received percutaneous coronary intervention (PCI) in the UK between 2006 and 2013. BCIS collects information related to PCI procedures in the UK. National Institute for Cardiac Outcomes Research (NICOR) manages the data collection and in 2015, the BCIS-NICOR database collected >99% of all PCI procedures performed. The BCIS-NICOR database contains 113 clinical, procedural and outcomes variables; a set of standard definitions are available publicly on the NICOR website (7). The BCIS standard dataset defines good LV function as LVEF > 50%, moderately impaired as an LVEF of 30 – 50% and poor LV function as < 30%. The definition allows LV function to be derived from echocardiography nuclear cardiology studies, cardiac magnetic resonance imaging or invasive left ventriculography. Diabetes status and type of diabetes were recorded by the PCI operator at the time of procedure as no diabetes, diabetes (diet controlled), diabetes (tablet controlled) or diabetes (insulin controlled). All entries are linked to mortality data recorded in the Medical Research Information Services via their unique identifier NHS number along with in-hospital major adverse cardiovascular events (MACE) and bleeding (8-10).

Patients were excluded if LV function or diabetic status was unknown. Data collected included age, sex, left ventricular ejection fraction, New York Heart Association (NYHA) class, smoking status, hypertension, hypercholesterolaemia, family history of coronary heart disease, previous myocardial infarction (MI), renal disease, previous PCI, previous coronary artery bypass graft (CABG), intra-aortic balloon pump use, receipt of ventilation, cardiogenic shock, thrombolysis use, radial access, diagnosis (unstable angina, Non-ST elevation MI (NSTEMI) and ST elevation MI), vessel attempted (left main, left anterior descending (LAD), circumflex, right coronary artery, graft), three vessel disease, multivessel disease, type of stent used (bare-metal stent (BMS), drug-eluting stent (DES)), number of stents and the outcomes death at 30 days, in-hospital MACE and in-hospital bleeding. MACE was defined by the composite of re-infarction, repeat PCI and death in-hospital. In-hospital bleeding was defined by a composite of gastrointestinal bleeding, cerebrovascular bleeding, receipt of blood or platelet transfusion, retroperitoneal bleed or bleeding requiring surgical intervention.

Data analysis was performed using Stata 14. Descriptive statistics were presented according to diabetes status and LV ejection fraction. One-way analysis of variance was used to determine if there were difference among groups for continuous variables and chi-squared test was used to determine if there were difference among groups for categorical variables. Multiple imputations with chained equations using the Stata function mi impute was used to impute missing values.

Univariable and multivariable logistic regressions were used to determine odds of 30-day mortality, in-hospital MACE and in-hospital bleeding according to left ventricular ejection fraction group among the subgroup of diabetic and non-diabetic participants. Multiple logistic regressions were adjusted for all baseline variables including diagnosis, age, hypertension, hyperlipidaemia, three vessel disease, multivessel disease, type of stent (BMS vs DES), sex, NYHA class, renal disease, previous myocardial infarction, previous PCI, previous CABG, family history of heart disease, smoking status, ventilation, cardiogenic shock, thrombolysis use, intra-aortic balloon pump use, radial access, target vessel and number of stents. The same models were used to evaluate adverse outcomes according to diabetes status and then diabetes treatment among subgroups of left ventricular dysfunction.

Sensitivity analyses were performed, where we excluded patients with cardiogenic shock, receiving ventilatory support or requiring intra-aortic balloon pump.

**Results**

A total of 588,639 PCI procedures were undertaken in England and Wales during the study period. Patients were excluded if diabetes (n=36,279) or LV function status (n=275,968) was not recorded. Figure 1 outlines the flow of patients within the analysis. Of the 260,726 included patients, DM was present in 52,160 (20%) with management status known in 51,469 (98.7%) - diet controlled in 9,047(17.5%), tablet controlled in 29,800 (57.9%) and insulin requiring in 12,622 (24.5%). Severe LVSD was present in 18,148 (7%), moderate LVSD in 51,266 (20%), with 191,312 (73%) having normal LV function. Figure 2 shows the time trends in prevalence of LV function and diabetic status by year for the study period.

Table 1 outlines the baseline characteristics between groups defined by diabetic status and LV function. There were significant differences in the baseline comparisons. Moderate LVSD and severe LVSD were more common in patients with prior MI, prior CABG, renal dysfunction and unstable clinical presentations (STEMI and NSTEMI) in both DM and non-DM patients. Indicators of critical illness, such as cardiogenic shock, IABP use and ventilation were also more common in patients with moderate and severe LVSD. For patients with poorer LV function was more common although, as with other baseline variables, the differences were more marked in patients with DM (Non DM 6%, 12%, 17% vs DM 9%, 19%, 26% for three vessel disease in normal LV function, moderate and severe LVSD respectively). Missing information about each variable is provided in the supplementary table 1 and 2.

**Crude outcomes by LV function, diabetes and sub-type of diabetes**

There was a trend for poorer unadjusted outcome with increasing grades of LV dysfunction in patients with both DM and non-DM (Table 2). Across all grades of LV dysfunction, there was a higher crude mortality rate in DM patients and within the DM cohort, insulin-requiring diabetes had worse outcomes as compared to diet and tablet controlled DM (Table 2).

**Effect of LV function on outcome**

Increasing degrees of LV dysfunction were associated with a poorer prognosis at 30 days following PCI (table 3a, figure 3a,3b). The adjusted rates of 30-day mortality for nondiabetics was increased to more than two-fold for moderate LVSD (Odds Ratio (OR) (95% confidence interval (CI)) 2.09 (1.90-2.31)), and more than four-fold for poor LV (OR 4.55 95% CI (4.09-5.06)) compared to patients with normal LV function. Among diabetic patients, the effect of LV dysfunction on mortality was very similar; moderate LVSD OR 2.03 (95% CI (1.73-2.38)) and poor LV OR 4.17 (3.52-4.93). Bleeding and MACE rates were also modestly increased with declining LV function, also with no clear differential effect between diabetic and non-diabetic patients.

**Effect of DM on outcome**

When outcome was assessed by diabetic status, there was an increase in mortality at 30 days for all grades of LV dysfunction (Table 3b). The relative effect of diabetes was attenuated in the poor (OR 1.34 (95% CI 1.17-1.52) and moderate (OR 1.38 (95% CI 1.21-1.57) LV function group compared with the normal LV function group (OR 1.62 (95% CI 1.41-1.86). Diabetes was not associated with MACE or bleeding after PCI with any grade of LV function.

**Outcome by DM sub-type**

Further analysis of the diabetes cohort by type of treatment suggested a greater association between diet-controlled DM with mortality at 30 days in poor LV function (OR 5.35 (95% CI 3.60-7.96) than was seen with those treated by either oral hypoglycaemic agent (OR 4.34 (95% CI 3.41-5.52) or insulin (OR 3.27 (95% CI 2.41-4.43) (table 4a, figure 4a,4b,4c). No clear subgroup differences were noted for the other outcomes of in-hospital bleeding or MACE.

When outcome was assessed in relation to LV function, the trend for a reduced influence of diabetes with reduction in LV function was again noted predominantly in insulin-treated patients (table 4b, figure 5a,5b,5c). For patients with diabetes, the requirement for insulin treatment had a greater influence on 30-day mortality where LV function was preserved (OR 2.09 (95% CI 1.66-2.65), compared to moderate (OR 1.56 (95% CI 1.26-1.93) or poor LV function (OR 1.40 (95% CI 1.13-1.74). This observation was not seen for diet-controlled DM. Following the removal of the highest risk patients (cardiogenic shock, IABP, ventilation) sensitivity analysis confirmed similar findings to the whole cohort (supplementary table 3).

**Discussion**

This analysis of 260,726 patients from the UK national dataset, confirmed the impact of LV systolic dysfunction on mortality at 30 days after PCI. Furthermore, this study showed that the relative influence of DM (in particular insulin-requiring patients) on early mortality after PCI was diminished in patients with the lowest LV ejection fractions. For the cohort as a whole, DM was associated with a modest but consistent increase in mortality at 30 days in all grades of LV dysfunction.

Previous analyses of the UK dataset have confirmed the strong relationship between reduced LV function and PCI outcomes(6). Studies in large populations have suggested that diabetes is an important risk factor for development of heart failure (4, 11), and worse long-term outcome in patients with established heart failure (4). In patients presenting acutely with STEMI, DM is associated with increased incidence of subsequent heart failure, and worse outcome (12). Following PCI, outcomes in patients with DM were poorer in the early stent (13), and pre-drug eluting stent (DES) eras (14). More recently DM was found to be a significant predictor of worse longer-term outcomes following PCI, particularly in incomplete revascularisation (15), and following primary PCI (16, 17).

Our data revealed that within the diabetic population, insulin requiring DM was associated with poorer outcomes regardless of LV function. Diabetic patients had worse risk factor profiles with increased incidence of hypertension and hyperlipidaemia, increasing the likelihood of concomitant microvascular disease. This cumulative disease burden significantly affects the risk of future cardiovascular disease in patients with type 2 DM both in the absence of known coronary disease (18) and following revascularisation (PCI or CABG) (19, 20). Both iatrogenic hyperinsulinaemia and the endogenous hyperinsulinaemic state present in type 2 diabetes, can promote pro-inflammatory responses affecting progression of atherogenesis and disrupting endothelial function along with increased platelet aggregation, increasing the risk of MACE events (21-23). Large contemporary DES trials support this observation, with increased rate of target lesion revascularisation (TLR) shown in insulin requiring patients. (24, 25). Our analysis of this very large real-world cohort, confirms the association between DM and a worse early PCI outcome in a contemporary population, treated predominantly with DES.

In the setting of severe LVSD, we found DM to be less important at predicting early PCI outcomes. It should be noted that DM was not protective in LVSD, and the worst crude outcomes following PCI are in the group of patients with poor LV and DM with the 12.7% of insulin-requiring DM and poor LV having the highest mortality at 30 days of any subgroup. The combination of DM and severe LVSD was associated with greater proportions of previous CABG, previous MI, renal disease, and lower rates of radial access, which may exert independent effects. However, after adjustment for known confounding factors the apparent doubling of risk in normal LV function patients seen with insulin requiring DM, was markedly lower in patients with severe LVSD.

The association between LV function and adverse mortality outcomes, and the differential association of poor LV function on mortality across different indications for PCI, is recognised (6). Impaired physiological reserve reduces the tolerability of haemodynamic or ischaemic compromise during PCI whilst, in the long term, impaired LV function increases mortality from progressive heart failure and ventricular arrhythmias. Including LV function into the SYNTAX II score significantly improved the models’ ability to predict 4-year outcomes whilst diabetic status did not (26). Although it was noted that more ‘severe’ diabetes, in particular the presence of proteinuria, may be captured through variables such as creatinine clearance (27).

In summary, this large retrospective analysis confirms the adverse impact of poor LV function on patients undergoing PCI. Importantly, this study suggests that the impact of diabetes mellitus on outcomes after PCI is more pronounced in the presence of preserved LV function and declines progressively with worsening LV function. In developing risk models for patients undergoing PCI (such as SYNTAX), the findings from this study can provide information to improve predictive accuracy. The findings will help inform physicians and patients about potential risks of PCI in patients with diabetes mellitus and LV dysfunction.

**Strengths**

The BCIS-NICOR database represents the pooled experience of almost all PCI in the UK NHS, and are collected to facilitate the national audit of practice and the public reporting of results. The data are collected prospectively and are genuinely representative of actual clinical practice across the whole country. The registry is a powerful resource given its scope, the consistency of definitions, completeness and routine availability of unbiased clinical outcomes. The present study is a secondary analysis of this data, an approach that has inherent strengths and weaknesses. The present study is a secondary analysis of this data, an approach that has inherent strengths and limitations.

The BCIS data reflecting real world experience, enhances the ability to analyse outcomes in

sub-categories of large numbers of patients and provides insight that would not be possible in

sub group analyses of existing randomised controlled trials, given that the small numbers of

diabetics with significant impairment in LV function recruited in trials.

Mortality tracking was complete for all patients included, and provides a robust and unbiased

end-point. The BCIS dataset includes high-risk patients who are often excluded from randomised controlled trials. As such this national analysis represents the only study of the influence of DM on the prognostic impact of LV function on PCI outcomes to date.

**Limitations**

Only half of all patients who underwent PCI had LV function documented. The exclusion of patients without assessment of LV function is a potential source of bias in determining patient outcomes, although the distribution of LV function is similar to those reported in previous analyses and the proportion of missing data for LV function was numerically similar irrespective of diabetes status (50.6% in patients without DM and 47.5% in patients with DM (28, 29). Our study uses LV ejection fraction cut-offs defined by the British Cardiovascular Intervention Society to define good, moderately impaired and poor LV function. Use of alternate cut-off values such as those advocated by the ACCF/AHA guidelines (30) may influence both the reported prevalence of LV dysfunction and its prognostic impact across patients with different DM status. Third, the BCIS dataset does not capture usage of medications that have been shown to improve the prognosis in patients with heart failure or devices such as cardiac resynchronization therapy (CRT) devices or implantable cardiac defibrillators (ICDs). Whilst any prognostic benefit of such therapies might only be evident at longer timeframes, we cannot rule out that differences in provision of such therapies in patients with poor LV function may contribute to the differences in outcomes that we report. As a routinely collected national registry, end points are not specifically adjudicated. MACE and bleeding events are largely self-reported and may vary between institutions for completeness (31). The aim of this analysis was to assess the impact of DM on short term PCI outcomes. We did not have longer term outcome data available, although this would be of interest in a future study. Whilst it is well known that effective management of DM is associated with improved patient outcomes, the BCIS dataset does not collect data on either hypoglycaemic agents or glycaemic control (32). We were not able to account for the potentially important effect of undiagnosed/untreated diabetes. Such patients would have been classified as non-diabetic and may have resulted in an underestimation of the effect of diabetes on clinical outcome.  Additionally, the dataset does not routinely collect data on the date of DM onset or the presence of diabetes related complications and, whilst it is well known that effective management of DM is associated with patient outcomes, the BCIS database does not collect data on either hypoglycaemia agents or glycaemic control.

Finally, our analysis is of observational data and cannot be used to infer causal relationships; despite the inclusion of multiple procedural and demographic factors, unmeasured confounders might account for some differences of outcomes observed.

**Conclusion**

Our analysis of 260,726 UK patients undergoing PCI procedures in the DES era suggests that diabetes mellitus is associated with worse outcomes following all PCI in all grades of LV dysfunction. The independent prognostic impact of diabetes is strongest in patients with normal LV function but reduces in patients with severe LV systolic dysfunction.

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**Conflict of Interest:**

All authors declare that they do not have any potential conflict of interest relevant to the work

submitted in this manuscript.

**Contributorship**:

AZ conceived the study and developed study protocol and analysis plan. CSK and EK analysed the data. MJ drafted the paper. All authors contributed in interpretation of results and in making an important contribution to the manuscript. AZ is the guarantor of all the work.

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**Figure legends:**

**Figure 1:** Sample size for analysis and sensitivity analysis

A) Poor LV function B) Good LV function

**Figure 2:** Left ventricular function in non-diabetes and diabetes patients according to year

**Figure 3:** Adjusted risk of adverse outcomes by diabetes status and left ventricular ejection fraction

**Figure 4:** Adjusted risk of adverse outcomes according to left ventricular ejection fraction within subgroups of types of diabetes

**Figure 5:** Adjusted Risk of adverse outcomes by type of diabetes within left ventricular ejection fraction groups