**Outcomes Following Percutaneous Coronary Intervention (PCI) in Saphenous Vein Grafts (SVG) with and without Embolic Protection Device**

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**Tweet:** “EPD use and outcomes in SVG PCI using UK data, shows similar in-hospital MACE, Stroke & short or long-term mortality, although lower IP mortality in EPD Group in PSM analysis”

**Abstract**

**Background**: There are limited, and discrepant, data on the clinical benefits of the adjunctive use of embolic protection devices (EPD) during PCI to SVG in the contemporary era.

**Methods & Results:** We formed a longitudinal cohort (2007-2014, n=20,642) who underwent PCI to SVG in the British Cardiovascular Intervention Society (BCIS) database. Clinical, demographical, procedural and outcome data were analysed by dividing into two groups; No EPD- PCI to SVG without EPD (n=17,730) and EPD Group – PCI to SVG with EPD (n=2,912). Patients in EPD Group were older, had more comorbidities & higher prevalence of moderate-severe left ventricular systolic dysfunction. Mortality was lower in EPD Group during hospital admission (0.70% vs 1.29%, P=0.008), at 30-days (1.44% vs 2.01%, P=0.04) but similar at one-year (6.22% vs 6.01%, P=0.67). Following multivariable analyses, no significant difference in mortality was observed during index admission (OR:0.71, CI 0.42-1.19, P=0.19), at 30 days (OR:0.87, CI 0.60-1.25, P=0.45) and one year (OR:0.92, CI 0.77-1.11, P=0.41) along with similar in-hospital MACE (OR:1.16, CI 0.83-1.62, P=0.39) & Stroke (OR:0.68, CI 0.20-2.35, P=0.54). In Propensity Score-Matched (PSM) analyses, lower inpatient mortality was observed in EPD Group (OR:0.46, CI 0.13-0.80, P=0.002) although the adjusted risk of the periprocedural no/slow flow phenomenon was higher in patients where EPD were used (OR:2.16, 1.71-2.73, P<0.001).

**Conclusion:** In this contemporary cohort, EPDs were used more commonly in higher risk patients but were associated with similar clinical outcomes in multi-variable analyses. Lower inpatient mortality was observed in EPD Group in univariable & PSM analyses.

**Key Words:** Embolic protection devices, Percutaneous Coronary Intervention, Saphenous Vein Grafts, Mortality, No flow**Condensed abstract**

There are limited contemporary data on the clinical benefits of the adjunctive use of embolic protection devices (EPD) during PCI to SVG. We analysed patients who underwent PCI to SVG in BCIS database from 2007-2014 by dividing into two groups; No EPD Group: PCI to SVG without EPD and EPD Group: PCI to SVG with EPD. Patients in the EPD Group were older and had more co-morbidities. Following multivariable analyses, in-hospital MACE, Stroke and short-or-long-term Mortality outcomes were similar between two groups. Lower inpatient mortality was observed in EPD Group in the PSM analysis.

**Abbreviations**

PCI: Percutaneous Coronary Intervention

SVG: Saphenous Vein Grafts

CABG: Coronary artery bypass graft

EPD: Embolic protection devices

MI: Myocardial Infarction

ACS: Acute Coronary Syndrome

ACC: American college of Cardiology

ESC: European Society of Cardiology

**Introduction**

Atherosclerotic plaques in saphenous vein grafts (SVG) contain more inflammatory cells, have little fibrous cap, are more diffuse and friable and have less calcification as compared to plaques in native atherosclerotic coronary arteries.(1) Due to these different characteristics, percutaneous coronary intervention (PCI) of SVG lesions are more prone to distal embolization resulting in angiographic no-reflow and distal microvascular obstruction. Several clinical studies have reported increases in both peri-procedural myocardial infarction and mortality in association with angiographic no reflow and microvascular obstruction.(2) To mitigate the risk of these complications, the adjunctive use of embolic protection devices (EPD) has been assessed in clinical studies,(3-5) thereby leading to a Class 1 (level of evidence B) recommendation in most recent American College of Cardiology / American Heart Association guidelines in setting of PCI to SVG.(6) Interestingly, these recommendations are primarily based on the data from only 1 randomized control trial (RCT), conducted in 1999-2000.(3) This trial demonstrated that EPD use in SVG intervention was associated with fewer major adverse cardiovascular events at 1 month, driven by lower rate of peri-procedural myocardial infarction (MI). Recently, the European Society of Cardiology (ESC) has downgraded its recommendation for the use of EPD from Class 1, level of evidence B in 2014 guidelines to Class IIa, level of evidence B in its 2018 revascularization guidelines.(7) Observational studies published in more contemporary cohorts around the use of EPD in SVG intervention have yielded conflicting results.(4,8-11) Brennan and colleagues analysed the National Cardiovascular Data Registry (NCDR) from 2005-2009 and found no outcome benefit in the routine use of EPD during SVG intervention and also observed higher periprocedural complications.(5) Despite several theoretical advantages of EPD use, these devices are relatively high profile and can be technically challenging to use. Moreover, in contemporary interventional cardiology practice, no-reflow and periprocedural MI during PCI to SVG have declined, (5) an observation that could be related to a number of factors including the adjunctive use of more potent antithrombotic therapy, image-guided optimisation of stents and thinner strut stent platforms.(12,13) Consequently, the role of the regular use of EPD in PCI to SVG has appropriately been questioned.(5,14) Therefore, we sought to describe the early (inpatient and 30 days) and late (1 year) outcomes of PCI in SVG, with and without the use of EPD, in a large contemporary unselected national cohort from the database of the British Cardiovascular Intervention Society (BCIS).

## **Methods**

We analysed national data for all patients that underwent PCI to SVG in England & Wales from January 2007 to December 2014. The British Cardiovascular Intervention Society (BCIS) records information on PCI practice in the UK with data collection managed by the National Institute of Cardiovascular Outcomes Research (NICOR). Recording of data is mandatory, as part of the formal revalidation process, for all independent PCI operators in the UK. The BCIS database are comprehensive and comprises of 113 clinical, procedural and outcomes variables with approximately 80,000 new records added each year.(15,16) We used data from the Office of National Statistics (ONS) for mortality tracking in all patients of England & Wales by using their unique National Health Service number. We excluded patients from Scotland and Northern Ireland because of the absence of the ONS-linked mortality data. Institutional research and ethical board approval were not required for this study as all data were anonymized and routinely collected as part of the national audit.

Data were gathered on patients’ clinical characteristics, risk profile and comorbid diseases as well as aspects of interventional practice and adjunctive pharmacological therapy. Data regarding all-cause mortality were collected during index admission and tracked up to one year after discharge. We also assessed in-hospital major adverse cardiovascular event (MACE; defined as a composite of in-hospital mortality, in-hospital myocardial infarction and target vessel revascularization), no reflow/slow flow phenomenon after PCI and in-hospital stroke which included ischaemic or haemorrhagic stroke or transient ischaemic attack (TIA). Furthermore, we analysed temporal changes in interventional practice for these patients from 2007-2014.

### **Statistical Methods**

The study participants were divided into two groups: (No EPD Group ) where no EPD were used during PCI to SVG, and (EPD Group) where EPD used during PCI to SVG. Patients with missing data for age, gender, and mortality follow up after discharge were excluded. For descriptive statistical analysis of demographics, procedural details, and unadjusted outcomes, continuous variables were reported as median and interquartile ranges, whereas categorical variables were reported using frequencies and proportions. Chi-square tests were applied to assess group differences for categorical variables, while rank sum test were used for continuous variables. We used multiple imputations with chained equations to impute data for all variables with missing information. The method is considered best practice when dealing with missing data, and can provide unbiased estimates even when levels of missingness are very high and also some protection when data are not missing at random. We applied multivariable logistic regression analysis to estimate the risk of adverse outcomes between groups. In multivariable analysis, we adjusted different covariates in the models included age, sex, smoking status, diabetes mellitus, hypertension, hyperlipidemia, previous myocardial infarction, previous stroke, peripheral vascular disease, family history of coronary artery disease, Left Ventricular systolic dysfunction (LVSD), clinical presentation (ST Segment Elevation Myocardial Infarction (STEMI) , Non ST Segment Elevation Myocardial Infarction (NSTEMI), Elective procedure), radial access site, glycoprotein IIb/IIIa inhibitor, Multiple territories attempted, Ventilatory Support, Circulatory support, the Drug-eluting stent use, number of stents, thrombus aspiration. We also performed Kaplan-Meier survival analysis and Cox proportional hazards regression analysis for 30-days and 1-year mortality. The proportional hazards assumption was assessed through Schnoenfeld’s residuals.

We also applied multiple imputations with propensity score matching (PSM) to estimate the average treatment effect, adjusting for baseline differences in the two groups of interest. One to one matching with replacements was applied, followed by logistic regression analysis (the sole predictor being group membership) to obtain the average treatment effect over the multiply imputed datasets. We used the nearest-neighbour matching method and no procedures were discarded. We used same variables as in our previous statistical analyses and the coefficients were converted to odds ratios to aid interpretation.

Stata 13.1 statistical package was used for all analyses. All statistical analyses were two-tailed, and an alpha of 5% used throughout.

## **Results**

### **Study cohort**

Our study cohort consisted of 20,642 patients who had PCI to SVG in England & Wales from January 2007 to December 2014. The process of patients’ inclusion and exclusion for this analysis is presented in Supplementary Figure 1. Out of 20,642 total patients who underwent PCI to SVG during this study period, EPD were used in 2,912 (14%) procedures. The median follow-up of the entire cohort was 4.12 (IQR 2.08 – 6.63) years. Moreover, we assessed temporal changes in interventional practice for these patients from 2007-2014 (Figure 1). Use of EPD was lowest in 2007 & 2008 (8% & 10%), highest in 2009 & 2010 (19%) and then decline steadily in subsequent years (2013:14%, 2014:13%).

## **Clinical characteristics**

There were significant differences observed in demographics, clinical and procedural characteristics between the two groups (Table 1). Specifically, patients with EPD use were significantly older, less likely to be female, had a higher prevalence of DM, hypertension, hypercholesterolaemia, previous MI or Stroke as compared to those in whom EPD devices were not used. More patients in the EPD Group (29 % vs 21%) received Glycoprotein IIb IIIa inhibitor possibly indicative of greater thrombotic burden and a higher risk profile in this group. In the no EPD group , a higher proportion of patients had cardiogenic shock (1.28% vs 0.66%, P=0.004) and needed mechanical ventilatory support (2% vs 1%, P= <0.0001). Use of EPD was lower in patients presenting with STEMI (7% vs 12%, P= <0.0001) or during elective PCI (34% vs 45%, P = <0.0001) but higher in patients with Unstable Angina/NSTEMI (59% vs 45%, P = <0.0001). The overall incidence of any procedural complication (Aortic dissection, Coronary perforation, Heart block requiring pacing, DC cardioversion, no flow/slow flow phenomenon, need ventilation, Shock induced by procedure) was higher in the EPD group as compared to the no EPD group (7.73% vs 4.68%, P = <0.0001). In Supplemental figures 2-4, we presented the use of EPD in different age categories, by gender and by the indication of procedure (STEMI, NSTEMI or elective).

Details about types of different embolic protection devices used during SVG PCI are presented in Supplement table 1. The most commonly used EPD were Spider devices were used in 45% of patients followed by Filter Wire in 41%. We observed heterogenous PCI practice in different regions, with more EPD use during SVG PCI in certain regions compared to others (Supplementary figure 5).

## **Clinical outcomes**

The unadjusted (i.e. crude) mortality was higher in the no EPD Group during index hospital admission (1.29% vs 0.70%, P=0.008) and at 30 days (2.01% vs 1.44%, P = 0.04) compared to the EPD Group , but was similar after one year of follow up (6.01% vs 6.22%, P = 0.67) (Table 2). The proportion of no flow/slow flow phenomenon was higher in the EPD group as compared to the no EPD group (5.1% vs 1.6%, P = <0.0001). The prevalence of in-hospital MACE and stroke were similar in both groups when baselines differences were not adjusted. In the central illustration figure we present unadjusted Kaplan-Meir survival estimates at follow up of one year and at final censorship date.

The adjusted risk of short- and long-term mortality, in-hospital MACE and strokes are presented in Table 3. In multivariate analysis, after adjustment of baseline dissimilarities, no significant differences in mortality were observed between groups during index admission (Odds ratio (OR) of the EPD Group: 0.71, CI 0.42-1.19, P = 0.19), at 30 days (OR 0.87, CI 0.60-1.25, P = 0.45) and at one year of follow up (OR 0.92, CI 0.77-1.11, P =0.41). In the multivariable statistical analysis, the risk of no reflow/slow flow was double in patients where EPD were used in PCI to SVG as compared to control group (OR: 2.16, 1.71-2.73, P = <0.0001). However, no significant differences in MACE and stroke were observed between the 2 cohorts (for MACE; OR 1.16, CI 0.83-1.62, P = 0.39 & for stroke; OR 0.68, CI 0.20-2.35, P = 0.54) after adjustment of baseline covariates. Similar results were observed irrespective of whether a complete case analysis was undertaken or multiple imputation methods for missing data were used. We performed a detailed sub-analysis after excluding those patients who underwent PCI to SVG and native coronary arteries during the same procedure and the results are presented in supplement table 2. Our findings did not materially change by excluding these cases.

## **Analysis with Propensity Score-Matching**

 In a propensity score matching analysis the adjusted risk of mortality during index admission was lower in the EPD group (OR 0.46, CI 0.13-0.80, P = 0.002) as compared to the no EPD group but was similar at 30 days (OR: 0.77, CI 0.34-1.22, P = 0.31) and one year (OR: 0.89, CI 0.62 – 1.18, P = 0.45). Similar to our previous analysis, the adjusted risk of no reflow/slow flow phenomenon was higher in PCI where EPD were used (OR: 2.29, CI 1.52-3.08, P = 0.001) as compared to control group. We did not observe any differences in other clinical outcomes like inpatient Stroke or MACE among patients with or without the use of EPD who underwent PCI for SVG (Table 4).

## **Risk of adverse outcomes in ACS patients only**

We also performed a multivariable analysis to assess the risk of adverse outcomes between the two groups among patients who presented with ACS (Table 5). No significant differences in a variety of clinical outcomes were observed (inpatient, 30 days & 1-year mortality, inpatient stroke or MACE); Table 5. However, the adjusted risk of no reflow/slow was higher in the EPD group (OR 1.90, CI 1.38 – 2.64, P = <0.0001) as compared to the no EPD group.

## **Risk of adverse outcomes by volume of EPD use in hospitals**

We also performed a series of Uni- and Multivariate analyses to assess impact of total EPD volume in given hospitals and their association with clinical outcomes. The total number of EPD usage in Saphenous Vein Grafts PCI during study period (2007-2014) in individual hospitals varied from 0 to 229. We divided hospitals into quartiles according to total volume of EPD usage (0-57, 58-114, 115-171 & 172-229) and unadjusted clinical outcomes are described in Supplement table 3. We observed similar results compared to previous analyses after inclusion of this variable in Multivariate statistical models on imputed data. We did not observe any difference in short or long-term mortality, in-hospital stroke or MACE (Supplement tables 4-8) associated with EPD uses in the higher volume quartile, and risk of no-flow or slow flow still remained significantly higher in the highest volume EPD group (OR 1.86, CI 1.38 - 2.52, P <0.001) (Supplement table 9).

## **Discussion**

Our study demonstrates EPD during PCI of SVGs are mainly used in older patients who have a higher burden of comorbid conditions in contemporary PCI practice. Lower inpatient mortality was observed in EPD Group in univariable & PSM analyses but not in Multi variate analysis. This discrepancy of results between two statistical methods is probably due to the presence of unmeasured confounding factors in the data. We observed a trend towards lower long-term mortality, in-hospital MACE & Stroke in the EPD group but these differences were not statistically significant in multivariable analyses. EPD use was associated with a higher adjusted risk of no reflow/slow flow phenomenon. To our knowledge, this is one of the largest contemporary studies to evaluate clinical outcomes of EPD use in patients undergoing PCI to SVGs.

Current guidelines recommending the use of EPD use are based on limited randomised controlled data derived nearly two decades ago, without evidence from more contemporary studies to support their continued in the contemporary era.(6) Indeed, a recently published meta-analysis suggested no benefit in the routine use of EPD during SVG intervention.(14) Interestingly, the Saphenous vein graft Angioplasty Free of Embolic Randomised (SAFER) Trial remains the only direct randomized comparison of embolic protection versus no embolic protection in PCI to SVG. The observed 42% relative reduction in major adverse cardiac events (a composite of death, myocardial infarction, emergency bypass or target lesion revascularization by 30 days) in the EPD arm in this trial was mainly driven by less MI (8.6% vs 14.7%, P = 0.008) and no “re-flow” phenomenon (3% vs 9%, P = 0.02), without any difference in mortality between two cohorts.(3) Furthermore, MI was defined in this study as an elevation of CK-MB fraction >3 times the upper limit of normal (standardized to each recruitment site normal range) in at least 1 of 3 serial cardiac enzyme measurements performed during the first 18-24 hours after the index PCI or in any later clinically indicated measurement. The limitations of this definition of MI are recognised and it has been updated with the recently published Fourth Definition of MI.(17) The Randomized, Controlled Trial of Saphenous Vein Graft Intervention with a Filter-Based Distal Embolic Protection Device (TRAP) trial was terminated early because of slow enrolment. However, this trial showed no significant reduction in the incidence of MI with use of EPD (10.5% vs 16.2%, P = 0.12.(8) Succeeding clinical trials of EPDs (including SpiderRx and FilterWire) designed on the contemporary relevance of the SAFER control cohort on non-inferiority basis.(8,18) Although data derived from these studies have demonstrated non-inferiority to existing EPD technology, they have not established evidence of the benefit of continued use of EPD technology in modern intervention practice.

In our study, patients with EPD use were significantly older, had higher prevalence of

co-morbid conditions and severe LVSD, and received more Glycoprotein IIb/IIIa inhibitor. These findings indicate that the EPD cohort were higher risk and probably have greater thrombotic burden that may confound our analyses. Unfortunately, the individual lesion risk characteristics, especially thrombus load, and age of graft is not recorded in BCIS dataset. Given the real world nature of this study, use of EPD in a particular lesion was at the discretion of the individual operator, and the reason that this technology was chosen cannot be wholly determined from the dataset available. The PSM analyses lacked key data such as SVG age, thrombus burden & imaging of conduits but still demonstrate statistically significant lower inpatient mortality in EPD group. It is highly possible that hidden confounders are not included in our statistical models. It is, therefore, possible that EPD are still effective in high-risk patients with adverse lesion characteristics like visible thrombus, long lesion length and high graft degeneration score. Considering the limitations of BCIS database, identification of a subset of cases involving these high-risk graft interventions was not possible.

Given the retrospective & non-randomized nature of this analysis, it could not have answered the question of whether EPDs should be a routine adjunct in all comers SVG PCI. The only randomized trial data of EPD use conducted over 20 years ago and supports the need for more data in the contemporary setting. More aggressive use of preprocedural, intraprocedural and postprocedural pharmacotherapy (including administration of more potent antiplatelet and vasodilators), better procedural techniques like direct stenting have potentially reduced periprocedural thromboembolic events, that may reduce the impact of distal embolic protection devices on a variety of clinical outcomes in contemporary interventional practice.(14,19-21) Alternatively, despite all risk adjustment during statistical analysis, the increased lesion level risk present in EPD cohort may have obscured the real benefit of these devices. Nevertheless, data derived from this study suggest that further more contemporary clinical data would be needed to identify cases that gain most benefit from the routine use of EPDs in SVG PCI.

In our study, EPD were used in a relatively small proportion (14%) of total SVG percutaneous intervention. This finding is consistent with other published observational data. For example, use of EPD limited to 21% in the National Cardiovascular Data Registry (NCDR) data analysis.(22) Furthermore, Brennan and colleagues reported that one-third of the centres in the US did not use EPD at all and only 5.6% used EPD in > 50% of PCI to SVG.(5) In a secondary temporal analysis we observed that the proportion of EPD use in SVG PCI was highest in 2009/2010 (19%) and steadily declined thereafter to 13% in 2014. The decline in use may have several explanations: i) current devices remain bulky, add complexity, and increase procedure duration ii) they may not be technically feasible for all cases because of the distinct anatomical profile of vein grafts lesions and may be challenging to deliver in severe graft stenosis iii) increased cost in the absence of clear evidence for patient benefit. It is also possible that contemporary data raised doubts about the benefits of EPD such that the technically demanding aspect of the procedure and added cost were not justifiable to many operators.

Despite advances in technology, the use of these devices is not free from complications. Brennan et al. reported in an analysis of US NCDR Cath PCI dataset from 2005-2009 that use of EPD was associated with higher incidence of procedural complications (including periprocedural MI, No reflow phenomenon, perforation and, dissection) without the reduction in short- & long-term mortality.(5) We also observed an increase prevalence of no flow/slow flow phenomenon EPD but it could be due to many reasons. It is remains unclear from the current analysis whether the increased risk of no flow/slow flow relates to the fact that EPD devices are probably to be used in cases with high thrombotic burden, or older more degenerate grafts that are associated with increases in the risk of no flow/ slow flow or whether it reflects embolization of material associated with delivery of these bulky devices.

## **Strengths & Limitations**

This analysis has several strengths. The BCIS dataset consists of an almost complete record of PCI procedures performed in the UK during the study period which provides unselected real-world insight, including high-risk patients with multiple comorbid conditions often not randomised in clinical trials, and represents one of the most extensive analyses of SVG PCI. To the best of our knowledge, no national cohort study has examined temporal trends of EPD use in PCI to SVG in the contemporary era of interventional practice. Furthermore, the large sample size of this study gives sufficient statistical power to accommodate differences in clinical outcomes between two cohorts.

This study also has several limitations. First, the comparisons performed between the two groups were not randomized; therefore, inferences may be confounded by unobserved differences in patients, procedures lesions across two groups. However, we attempted to overcome this inherent limitation by performing propensity score matching which is a recognised statistical technique in observational studies. Secondly, although mortality tracking within England & Wales is well structured, all clinical outcomes and post-procedural complications are self-reported without formal adjudication. Hence, such clinical outcomes are vulnerable to reporting biases, and complications might be underreported, although it is unlikely that there will be differences in such reporting biases in two studied groups. Thirdly, adjunctive glycoprotein IIb/IIIa inhibitors were administrated in 21% of patients included in this study. The benefit of routine glycoprotein IIb/IIIa inhibitors use in vein grafts PCI is unclear, and risk of bleeding is greater when current dosing regimens combine with the transfemoral approach.(6) We adjusted for this difference by multivariate analysis. Finally, though the majority of PCI might be performed in saphenous vein grafts, BCIS dataset do not record information about nature of grafts separately (arterial or venous). However, it is previously reported in NCDR data analysis that arterial grafts represented only 2.5% of all PCI procedures undertaken in bypass grafts in the US.(23)

## **Conclusion**

Our study demonstrates that EPD were used approximately one in six patients undergoing PCI to SVG. EPD were used in older patients who had more comorbid conditions and severe LVSD. Lower inpatient mortality was observed in univariate & PSM analysis but not in Multi variate analysis. Adjusted lower inpatient mortality was observed in PSM analysis when EPD were used in SVG PCI. EPD use is associated with more periprocedural no flow/slow flow phenomenon which may relate to selection bias, where EPD are used in cases with higher thrombus burden or degenerate or older grafts. Given advances in stent design and more potent antithrombotic regime use since original EPD trials were performed, more contemporary data are needed for identification of the subset of patients which would gain most benefit from EPD use in SVG PCI.

**Perspective:**

**What’s Known**

There are limited contemporary data about outcomes of the adjunctive use of embolic protection devices (EPD) during Percutaneous Cutaneous Intervention to Saphenous Vein Grafts (SVG).

**What’s new**

After adjustment for baseline differences, EPD use was associated with the presence of the periprocedural no flow/slow phenomenon, but had no impact on clinical outcomes, including mortality

**What’s next**

Contemporary clinical data would be needed for identification of the subset of patients which would gain most benefit from EPD use in SVG PCI.

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**Figures**

**Figure 1**: Temporal Pattern of EPD practice in Bypass Grafts PCI from 2007-2014

**Legend**: Yearly average use of Embolic protection devices in total SVG PCI from 2007-2014

PCI; Percutaneous Coronary Intervention, EPD; Embolic protection devices

**Figure 2: Central Illustration Figure** (KM survival estimates at 1 year)

**Legend:** Plot of survival function for EPD use versus No EPD use in SVG PCI

PCI; Percutaneous Coronary Intervention, EPD; Embolic protection devices, HR; Hazard ratio, CI; Confidence interval, KM; Kaplan Mier