Coronary perforation complicating percutaneous coronary intervention in patients presenting with an acute coronary syndrome: an analysis of 1,013 perforation cases from the British Cardiovascular Intervention Society database

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Abstract

Background: The evidence base for coronary perforation occurring during percutaneous coronary intervention in patients presenting with an acute coronary syndrome (ACS-PCI) is limited and the specific role of acute pharmacology in its clinical presentation unclear. **Methods and Results:** Using the BCIS PCI database, data were analysed on all ACS-PCI procedures performed in England and Wales between 2007 and 2014. Multiple regressions were used to identify predictors of coronary perforation and its association with outcomes. Propensity score matching was used to evaluate the association between differing P2Y12 inhibitors or glycoprotein inhibitors (GPI) and CP. During 270,329 ACS-PCI procedures, 1,013 coronary perforations were recorded (0.37%) with a stable annual incidence. In multiple regression analysis, covariates associated with increased frequency of coronary perforation included age, female gender, CTO intervention, number and length of stents used, and rotational atherectomy use, whilst differing P2Y12 inhibitors were not predictive. Using propensity score matching, use of a GPI was independently associated with tamponade (OR 1.50, [1.08-2.06], p=0.014). The adjusted odds ratios for all clinical outcomes were adversely affected by coronary perforation. **Conclusions:** Coronary perforation is an infrequent event during ACS-PCI but is closely associated with adverse clinical outcomes**.** GPI use was associated with higher rates of tamponade.

Keywords

Coronary perforation, acute coronary syndrome, percutaneous coronary intervention, complications, tamponade, anti-platelet therapy, glycoprotein inhibition

1. INTRODUCTION

Coronary perforation is a rare but serious complication of percutaneous coronary intervention (PCI) with an incidence of ~0.4% of all PCI cases [1-6]. Recently we published a national analysis of the temporal trends, predictors and outcomes of coronary perforations in the United Kingdom and reported that increasing patient age, previous coronary artery bypass surgery (CABG), and chronic total occlusion PCI (CTO-PCI) were the strongest independent predictors of coronary perforation during PCI [7]. However, non-ST elevation myocardial elevation (NSTEMI) presentation was also independently associated with an increased incidence of perforation. In light of this, and also because acute coronary syndrome PCI (ACS-PCI) now accounts for the majority of all PCI procedures undertaken worldwide, a more in depth understanding of the predictors and outcomes of coronary perforation during ACS-PCI is warranted.

In patients presenting with an acute coronary syndrome and undergoing PCI, the need for aggressive oral anti-platelet therapy with or without additional intra-venous anticoagulation therapy, whilst effective in reducing acute procedural thrombotic complications, might increase the risk of bleeding and potentially coronary perforation occurring and/or the severity of its clinical manifestations [7]. In the recent BCIS analysis of all PCI procedures, although glycoprotein inhibitor (GPI) use was associated with a lower incidence of coronary perforation in univariate analysis, use of a GPI was associated with higher 30-day mortality in those patients who experienced a coronary perforation [8]. Furthermore, in the same BCIS study, we observed differential effects on the incidence of coronary perforation with respect to three P2Y12 inhibitors. However, the BCIS perforation study included all clinical presentations, and therefore any observations with respect to ACS pharmacology and coronary perforation might be weakened by the inclusion of heterogeneous patient groups.

Therefore, the primary objective of this study was firstly to define the incidence, temporal trends, predictors and outcomes of coronary perforation associated with PCI in patients presenting with an

acute coronary syndrome through analysis of a national PCI database. Secondarily, the study also examines the interaction between oral P2Y12 inhibitors and intravenous glycoprotein inhibitor in the occurrence and clinical manifestations of coronary perforation during ACS-PCI.

2. METHODS

2.1 Study design, setting and participants

We retrospectively analysed national data from all patients undergoing ACS-PCI in England and Wales between January 2007 and December 2014. During the study period, a total of 669,280 patients underwent PCI. Patients were excluded from the analysis if they underwent PCI for stable angina, and if data were missing on anti-platelet therapy, glycoprotein inhibitor use or coronary perforation status (Supplementary Figure 1). The study was approved by review board of the National Institute of Clinical Outcomes Research and by the Healthcare Quality Improvement Partnership (HQIP).

2.2 Setting, data source, and study size

Data on PCI practice in the United Kingdom were obtained from the British Cardiovascular Intervention Society (BCIS) dataset that records this information prospectively and publishes this information in the public domain as part of the national transparency agenda [9]. The data collection process is overseen by The National Institute of Cardiovascular Outcomes Research (NICOR) (http://www.ucl.ac.uk/nicor/) with high levels of case ascertainment. The BCIS-NICOR database contains 121 clinical, procedural and outcomes variables, and in 2014, 98.6% of all PCI procedures performed in the National Health Service hospitals in England and Wales (www.bcis.org.uk/) were recorded on the database with approximately 100,000 new records currently added each year. The accuracy of and quality of the BCIS dataset has previously been ascertained [10]. Entry of all PCI procedures by UK interventional operators is mandated as part of professional revalidation. The participants of the database are tracked by the Medical Research Information Services for subsequent mortality using the patients' NHS number (a unique identifier for any person registered within the NHS in England and Wales). Although the BCIS dataset is UK wide, the participants of 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, and therefore only patients from England and Wales have mortality data available.

2.3 Study definitions

We analysed all recorded ACS-PCI procedures that were undertaken in England and Wales between January 1st, 2007 and December 31st, 2014. Coronary perforation was defined as in the BCIS guidance document as evidence of extravasation of dye or blood from the coronary artery during or following an interventional coronary procedure. Other study definitions were used as in the BCIS-NICOR database. Specifically, pre-procedural renal failure is defined as any one of the following: creatinine >200μmol/l, renal transplant history, or dialysis. Pre- or post-PCI disease severity was defined as a stenosis ≥70% in the case of the LAD, circumflex or right coronary arteries, or ≥50% in the case of the left main artery. Intravascular imaging was a combination of intravascular ultrasound and optical coherence tomography. An access site complication was defined as either a false aneurysm, haemorrhage (without haematoma), haemorrhage with delayed hospital-discharge, retroperitoneal haematoma, arterial dissection, or any access site complication requiring surgical repair. The clinical outcomes examined were in-hospital mortality, in-hospital MACCE (defined as a combination death, peri-procedural stroke, or peri-procedural myocardial infarction after PCI), in-hospital major bleeding (defined as either gastrointestinal bleed, intra-cerebral bleed, retroperitoneal haematoma, blood or platelet transfusion, access site haemorrhage, or an arterial access site complication requiring surgery), in-hospital re-infarction, in-hospital emergency cardiac surgery, tamponade, and 12-month mortality.

2.4 Data analyses

Statistical analysis was performed using Stata v14.0 (College Station, Texas, USA). Missing data is presented in Supplementary Table 1. Multiple imputations using the *mi impute* command were used to reduce the potential bias from missing data, assuming missing at random mechanisms. We used chained equations to impute the data for all variables with missing information and generated 10

datasets to be used the analyses. We examined the baseline and procedural characteristics of participants by coronary perforation status We tested for associations between each categorical variable and coronary perforation using a Chi-squared test, and for continuous variables we used one-way analysis of variance.

The crude number and annualized incidence of coronary perforations were explored graphically according to year of PCI. Similar graphical methods were used to depict the annual incidence of cardiac tamponade, transfusion, emergency CABG, major bleeding, in-hospital death and in-hospital MACE among patients with coronary perforation. A multiple logistic regression model was developed to identify variables associated with coronary perforation. The potential predictor variables in the model included age, sex, body mass index, smoking, hypertension, previous stroke, peripheral vascular disease, renal disease, previous MI, EF<30%, previous CABG, previous PCI, diabetes, year, operator status, vessel of PCI, no. of vessels, CTO attempted, no. of stents, STEMI, Q wave on ECG, cardiogenic shock, recent lysis, GPI use, clopidogrel, prasugrel, bivalirudin, radial access, dual access, largest balloon/stent, longest balloon/stent, embolic protection device, thrombectomy, rotational atherectomy, imaging, penetration catheter, laser atherectomy and micro-catheter. To specifically evaluate the association between different P2Y12 inhibitors, and between use or not of IV glycoprotein inhibition and the incidence of coronary perforation we used propensity score matching. The multiple imputations propensity score matching algorithm (mi estimate: teffects psmatch command in Stata) was used to estimate the average treatment effect. Four propensity score matched models were developed to evaluate coronary perforations which where: i) GPI vs no GPI, ii) prasugrel vs clopidogrel, iii) ticagrelor vs clopidogrel and iv) prasugrel vs ticagrelor. All variables used in the multiple logistic regression models were considered in the propensity score matching models excluding those variables which led to model non-convergence.

We also used a multiple logistic regression model to evaluate the independent variables associated with tamponade. Variables included in this model for tamponade included age, sex, body mass index, smoking, hypertension, previous stroke, peripheral vascular disease, renal disease, previous MI,

EF<30, previous CABG, previous PCI, diabetes, year, operator status, vessel of PCI, no. of vessels, CTO attempted, no. of stents, STEMI, Q wave on ECG, cardiogenic shock, recent lysis, GPI use combined, abciximab, eptifibatide and tirofiban separately, clopidogrel, prasugrel, bivalirudin, radial access, dual access, largest balloon/stent, longest balloon/stent, thrombectomy, imaging, and penetration catheter.

Multiple logistic regression models were developed to determine the influence of coronary perforation on the independent odds of emergency cardiac surgery, transfusion, in-hospital major bleeding, peri-procedural myocardial infarction, arterial complication, acute kidney injury, in-hospital major adverse cardiovascular events, in-hospital death and 12-month death. All variables in the previously described multiple logistic regression models were included as potential variables in the models aside from variables which led to non-convergence in the models. Survival analysis was performed up to 12-month for patients who had coronary perforation compared to those without using Kaplan-Meier survival curves, log-rank test and Cox regression**.** Finally, we used multiple logistic regression to evaluate the independent variables associated with predictors of 30-day mortality in those patients who experienced a coronary perforation. The potential predictor variables in this model included age, sex, body mass index, smoking, hypertension, previous stroke, peripheral vascular disease, renal disease, previous MI, EF<30%, previous CABG, previous PCI, diabetes, year, operator status, vessel of PCI, no. of vessels, CTO attempted, no. of stents, Q wave on ECG, cardiogenic shock, ventilation, recent lysis, GPI use, clopidogrel, prasugrel, bivalirudin, radial access, dual access, largest balloon/stent, longest balloon/stent, thrombectomy, rotational atherectomy, imaging, penetration catheter, laser atherectomy and micro-catheter.

3. RESULTS

3.1 Incidence of coronary perforation and baseline demographics during ACS-PCI by perforation status

During the study period, a total of 669,280 patients underwent PCI for any indication. After exclusions, 270,329 patients undergoing ACS-PCI who had complete data regarding antiplatelet and glycoprotein

inhibitor data were included in the analysis (Supplementary Figure 1). In total, 1,013 coronary perforations were recorded during ACS-PCI procedures giving an overall incidence of 0.37%. There were 157 coronary perforations in patients treated with abciximab, 58 in those treated with tirofiban, and 55 in those treated with eptifibatide. Although the crude numbers of coronary perforation increased from 77 in 2007 to 188 in 2014, (Supplementary Figure 2 grey bars) this reflects an increase in ACS-PCI volume in England and Wales during the study period rather than a significant increase in coronary perforation incidence (p=0.36 for trend, Supplementary Figure 2 open circles). The baseline characteristics of patients with and without coronary perforation are presented in Supplementary Table 2. Coronary perforation was associated with increasing patient age and female sex, increased associated comorbidity (including hypertension, prior MI or stroke, peripheral vascular disease, low ejection fraction chronic anti-coagulation and renal disease), and previous coronary revascularisation with PCI or CABG. Pre-treatment with prasugrel, and presentation with ST elevation (with or without thrombolysis) were associated with a lower incidence of coronary perforation.

3.2 Procedural variables during ACS-PCI by perforation status

The procedural variables for patients with and without coronary perforation by vessel type are presented in Supplementary Table 3. Baseline disease complexity was associated with coronary perforation with more vessels and lesions attempted, a non-trainee primary operator, femoral or dual arterial access, CTO intervention, rotational atherectomy, laser atherectomy, intra-vascular ultrasound, and micro-catheter use all more frequently observed when perforation occurred. Coronary perforation was associated with left main artery, right coronary artery or graft PCI, and with more stents of a larger diameter and longer length. Coronary perforation was less likely when thrombus aspiration or a glycoprotein inhibitor were used.

3.3 Predictors of coronary perforation during ACS-PCI in England and Wales 2007-2014

Using multiple regression, covariates found to be associated with coronary perforation during ACS-PCI are presented by vessel in Table 1. The only patient-related factors associated with an increased incidence of perforation were age per year (odds ratio (OR) 95% confidence intervals 1.03 [1.03-1.04],

p<0.001), and female gender (OR 1.28 [1.08-1.51], p=0.004). Several procedural factors were associated with an increased incidence of vessel perforation including CTO intervention (OR 3.08 [2.44-3.89], p<0.001), dual arterial access (OR 1.85, [1.39-2.47], p<0.001), left main PCI (OR 1.46, [1.00-2.12], p<0.001), vein graft PCI (OR 2.54, [1.53-4.22], p=0.002), number of stents used per case (OR 1.35, [1.25-1.45], p<0.001), longest stent used per mm (OR 1.01, [1.01-1.02], p<0.001), micro-catheter use (OR 1.97, [1.04-3.73], p=0.37), and rotational atherectomy use (OR 1.88 [1.29-2.74], p=0.001). Diabetes mellitus (OR 0.75 [0.60-0.92], p=0.006), and a trainee first operator (OR 0.75, [0.61-0.89], p=0.002) were associated with a lower incidence of coronary perforation (Table 1). In multiple regression analysis, differing P2Y12 inhibitors were not associated with an increased frequency of coronary perforation. Using propensity score matching to evaluate the association between differing P2Y12, prasugrel was associated with a lower incidence of perforation compared to clopidogrel (p=0.007) and compared to ticagrelor (p=0.022, Supplementary Table 4). Glycoprotein inhibitor use was not associated with an excess of coronary perforation when propensity score matching was used (p=0.088, Supplementary Table 4).

3.4 Clinical outcomes by perforation status

All immediate procedural complications including cardiogenic shock induction, heart block, coronary dissection and major side branch occlusion were more likely when a coronary perforation occurred (Supplementary Table 5). In total, an additional acute coronary complication occurred in 41.1% of patients suffering a coronary perforation. Tamponade leading to haemodynamic compromise occurred in 29.6% of patients although emergency reparative cardiac surgery was undertaken rarely (2.5%). However, there was a significant reduction in the occurrence of tamponade and the need for cardiac surgery over the study period (Figure 1, upper panels, p<0.001 for both trends). Using multiple regression analysis, the independent predictors of tamponade included age per year (OR 1.07, [1.05-1.08], p<0.001), number of stents per stent (OR 1.48, [1.30-1.68], p<0.001), CTO-PCI (OR 2.26, [1.40-3.65], p=0.001), and maximum balloon/stent length per mm (OR 1.01, [1.00-1.02], p<0.001). Use of any glycoprotein inhibitor was also independently associated with tamponade (OR

1.50, [1.08-2.06], p=0.014) (Table 2). A history of previous CABG and trainee first operator were associated with a lower incidence of tamponade.

Crude in-hospital clinical complications are listed in Supplementary Table 4 and indicate that coronary perforation very significantly affected the morbidity and mortality of patients undergoing ACS-PCI. However, as indicated in Figure 1 there were significant reductions in transfusion, major bleeding and in-hospital MACE throughout the study period. The adjusted odds ratios for adverse clinical outcomes are presented in Table 3 with emergency cardiac surgery (OR 27.52, [14.09-53.72], p<0.001), transfusion (OR 14.27, [6.67-30.52], p<0.001), in-hospital major bleeding (OR 6.57, [4.88-8.85], p<0.001), in-hospital death (OR 8.13, [6.29-10.51], p<0.001), and in-hospital MACCE (OR 8.05, [6.42-10.09], p<0.001) all significantly associated with coronary perforation. Using multiple regression analyses, the independent associates of 30-day mortality included age, shock or ventilation on presentation, and renal disease (Supplementary Table 6). Use of any glycoprotein inhibitor was not independently associated with death at 30 days (OR 1.58, [0.86-2.92], p=0.143). Finally, coronary perforation was associated with an excess of 12-month mortality (hazard ratio 1.96 [1.57-2.43] p<0.001). Supplementary Figure 3 illustrates the Kaplan Meier plots for mortality by perforation status to 12-months confirming the significant impact of a perforation on patient survival to 12-months. The association between perforation and adverse 12-month survival was confirmed by log-rank testing and Cox regression.

4. DISCUSSION

This analysis found an overall incidence of coronary perforation in patients undergoing ACS-PCI of 0.37%, a rate similar to a general PCI population previously reported from the BCIS National PCI Database [8]. However the observed frequency in the current study was lower than more complex patient cohorts such those undergoing PCI with previous CABG (0.68%) or for CTO disease (1.40%) from data also derived from the BCIS PCI registry [11, 12]. The risk factors for coronary perforation in the current study included increasing patient age, CTO intervention, dual arterial access, left main PCI

and use of rotational atherectomy and were amongst the most important independent associates. These risk factors most likely represent the complexity of the coronary disease with calcific, occlusive vessels requiring aggressive interventional strategies to achieve procedural success. Indeed, in other previous examining coronary perforation as a complication of CTO-PCI, the overall incidence of perforation was significantly higher than in a less selected PCI population [13-14]. Additionally, in the BCIS CTO analysis, was a step-wise increase in the frequency of coronary perforation as the interventional strategy became more complex [11]. Whilst operators will try and minimise the risk of perforation during such high-risk procedures, in most circumstances, their occurrence is unpredictable. These data are important to enable a fully informed consenting process particularly for complex ACS-PCI cases, and also highlight the need for pre-procedural planning, familiarisation with the all components of the interventional tool-box, and a clear plan of action should such a complication occur.

Although there was no increase in the overall incidence of coronary perforation as a percentage of total ACS-PCI cases during the study period, crude numbers increased as the numbers of ACS-PCI increased in the United Kingdom. However, it is encouraging to observe that tamponade and surgical repair rates declined steadily during the study period. The development of tamponade inevitably results in the need for pericardial drain which has well-recognised risks even in an elective situation [15]. These include puncture of cardiac chambers/vessels and other organ puncture or bleeding, and there are numerous series and case reports of catastrophic consequences of pericardiocentesis in the literature [16-18]. The performance of pericardiocentesis in the peri-arrest situation is also undoubtedly an extremely challenging procedure and the risks likely to contribute to subsequent patient morbidity and mortality. Therefore, newer techniques such as ping-pong dual guide-catheters have significantly improved the acute management of coronary perforations and are likely to have contributed to the lower rates of tamponade and improved MACE [19-21]. Other developments in interventional equipment have also likely contributed to improved outcomes. One example is the embolisation coil which in recent years have become straightforward to deliver, and are effective in the timely treatment of guidewire exit perforations and septal perforations [22-24]. Additionally, the

development of more deliverable covered stents has meant that perforations in calcific vessels can now be more reliably sealed percutaneously obviating the need for emergency cardiac surgery [25-28]. Lower profile more deliverable covered stents have also facilitated a "block and deliver" technique where an occlusive balloon and a covered stent are delivered simultaneously down an 8F guide-catheter [29]. However, despite these technical and procedural advances, mortality and overall major adverse events in patients with coronary perforation remain high and serve as a reminder that whilst coronary perforation during ACS-PCI is a relatively rare event, its occurrence is associated with poor outcomes.

In the propensity matched analysis, prasugrel was associated with a lower incidence of coronary perforation compared to clopidogrel or ticagrelor. By contrast, in the ACCOAST randomised trial, preloading with prasugrel compared to prasugrel loading in the catheterisation lab was associated with an excess of major bleeding [30, 31]. The ACCOAST data potentially highlighted possible increased peri-procedural bleeding risks associated with potent P2Y12 inhibitors. One explanation for the differential results of ACCOAST compared to the current analysis might be differences in the study population. Prasugrel use in the United Kingdom is almost exclusively used in the primary PCI setting. Previous data demonstrating significant delays in platelet inhibition in the acute ST elevation scenario, and therefore oral P2Y12 inhibitors will not be fully biologically active at the time of PCI [32,33]. As such, differing P2Y12 inhibitors would not affect the peri-procedural risk of an acute coronary perforation or pericardial bleeding. In contrast, ACCOAST was undertaken in a NSTEMI population where oral absorption of P2Y12 inhibitors is still relatively effective. Indeed, rapid platelet inhibition was noted in the pre-loading arm of the ACCOAST study [30]. Additionally, there may be confounders in the propensity matched analysis which could not be completely corrected for and these unmeasured confounders may explain differences between studies. The contrasting results between the propensity matched analysis (where prasugrel was associated with a lower rate of coronary perforation than clopidogrel or ticagrelor) and the multiple regression analysis (where there was not an association between prasugrel and coronary perforation) may also be explained by unmeasured confounders. Within its UK licence, prasugrel is usually prescribed to younger, lower risk

patients i.e. to patients whose baseline likelihood of perforation is lower, and this variable baseline risk may not have been fully corrected for in the propensity matched analysis compared to clopidogrel or ticagrelor [34].

Several observations with respect to glycoprotein inhibitor use and coronary perforation from the current study are worthy of further comment. The lack of an excess of coronary perforation with glycoprotein inhibitor use - either when analysed as a group or individually - is perhaps unexpected but might be explained by interventional cardiologists adjusting their PCI strategy in the knowledge of potent intravenous anti-platelet therapy. Additionally, a coronary perforation may simply be a mechanical event and occurs regardless of the level of platelet inhibition if the dilatation forces and vessel wall interact in such a fashion to lead to rupture. These data are consistent with previous studies which did not identify an excess of coronary perforation with abciximab use albeit in modest sized studies [35]. However, the current data suggests that glycoprotein inhibitor uses increase the likelihood of tamponade once a perforation has occurred. This is an important finding of the study and in practice should encourage operators to have a low threshold for a placement of pericardial drain should even a small perforation occur when a GPI has been administered, or at the very least, observe the patient extremely closely.

The size of the current analysis also enabled a multiple logistic regression analysis of the predictors of 30-day mortality. The results are largely intuitive with increasing age, cardiogenic shock and renal disease all strongly predictive of increased mortality. Notably, this analysis also supports the anecdotal experience that if a coronary perforation does occur, concomitant peri-procedural use of a glycoprotein inhibitor is associated with adverse outcomes, with a 60% increase in 30-day mortality compared to no glycoprotein inhibitor use. These observations are important to consider particularly when undertaking ACS-PCI in elderly patients with calcific or occlusive coronary disease where the likelihood of coronary perforation is undoubtedly higher.

5. LIMITATIONS

Firstly, the timing of administration of P2Y12 inhibitors is not captured in the BCIS database and therefore we cannot provide specific information regarding this. However, in the majority of ACS patients, P2Y12 inhibitor loading would take place immediately on arrival to hospital. Secondly, the BCIS database does record not differentiate between coronary perforations resulting from guide-wire and those perforations due to balloon or stent inflation. Thirdly, the database does not record the Ellis classification of coronary perforation so that a sub-stratification by perforation severity was not possible in this series. Fourthly, the BCIS database does not record use of other treatment strategies such covered stents, pericardial drains or embolisation techniques and therefore data on outcomes with respect to different therapies is not available. Finally, because of the observational nature of this study, any conclusions may be influenced by unmeasured confounders such as frailty or anatomical considerations. These factors in particular might influence any associations between perforation and GPI use.

6. CONCLUSIONS

Coronary perforation is an infrequent event during ACS-PCI but is closely associated with adverse clinical outcomes**.** In multiple regression analysis, covariates associated with an increased frequency of coronary perforation included age, female gender, CTO intervention, number and length of stents used, and rotational atherectomy use, whilst differing P2Y12 inhibitors were not associated with an increased frequency of coronary perforation. Glyoprotein inhibitor use was associated with higher rates of acute tamponade.

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CONFLICTS OF INTEREST

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FIGURE LEGENDS

Figure 1: Upper row - Trends in the incidence of tamponade, transfusion and emergency CABG after coronary perforation during ACS-PCI 2007-14 in England and Wales ($p<0.001$ for all trends); Lower row - Trends in the incidence in-hospital major bleeding, death and MACE after coronary perforation during ACS-PCI 2007-14 in England and Wales ($p<0.001$ for major bleeding and MACE trends, trend non-significant for death).

SUPPLEMENTARY FIGURE LEGENDS

Figure 1: Patient study flow

Figure 2: Dark grey bars – Crude numbers of coronary perforation during ACS-PCI 2007-14 in England and Wales ($p<0.001$ for trend); Open circles – Annual incidence of coronary perforation during ACS-PCI 2007-14 in England and Wales ($p=0.37$ for trend).

Figure 3: Kaplan-Meier curves for survival to 12-months for patients by coronary perforation status following ACS-PCI in England and Wales.

Table 1: Multiple regression model of the significant associations between covariates and coronary perforation in patients undergoing ACS-PCI in England and Wales 2007-2014

Variable	Odds ratio	[95% CI]	p-value
Age (per year)	1.03	[1.03-1.04]	<0.001
CTO attempted	3.08	[2.44-3.89]	<0.001
Dual arterial access	1.85	[1.39-2.47]	<0.001
Vessel of PCI			
Vein graft	2.54	[1.53-4.22]	0.002
Left main	1.46	[1.00-2.12]	<0.001
Longest balloon/stent per mm	1.01	[1.01-1.02]	<0.001
No. of stents per stent	1.35	[1.25-1.45]	<0.001
Rotational atherectomy	1.88	[1.29-2.74]	0.001
Female sex	1.28	[1.08-1.51]	0.004
Micro-catheter	1.97	[1.04-3.73]	0.037
Diabetes	0.75	[0.60-0.92]	0.006
Trainee first operator	0.74	[0.61-0.89]	0.002

The multiple logistic regressions models were adjusted for more variables than those shown. Only variables with p-values <0.05 are shown in the table above.

Table 2: Multiple regression of independent predictors of tamponade during ACS-PCI in England and Wales 2007-2014

Variable	Odds ratio	[95% CI]	p-value
Age (per year)	1.07	[1.05-1.08]	<0.001
No. of stents (per stent)	1.48	[1.30-1.68]	<0.001
CTO attempted	2.26	[1.40-3.65]	0.001
Any GPI	1.50	[1.08-2.06]	0.014
Longest balloon/stent	1.01	[1.00-1.02]	0.043
Radial access	0.72	[0.53-0.99]	0.041
Trainee first operator	0.57	[0.39-0.83]	0.004
Previous CABG	0.17	[0.05-0.55]	0.003

The multiple logistic regressions models were adjusted for more variables than those shown. Only variables with p-values <0.05 are shown in the table above.

Table 3: Adjusted odds ratios of adverse clinical outcomes by coronary perforation status in patients undergoing ACS-PCI in England and Wales 2007-2014

Variable	**Adjusted odds ratio**	**[95% CI]**	**p-value**
Emergency cardiac surgery	27.52	[14.09-53.72]	<0.001
Transfusion	14.27	[6.67-30.52]	<0.001
In-hospital major bleed	6.57	[4.88-8.85]	<0.001
Peri-procedural MI	4.66	[2.79-7.79]	<0.001
Arterial complication	2.98	[1.93-4.59]	<0.001
Acute kidney injury	2.86	[1.16-7.07]	0.022
In-hospital MACCE	8.05	[6.42-10.09]	<0.001
In-hospital death	8.13	[6.29-10.51]	<0.001
12-month death	8.88	[6.75-11.69]	<0.001

Supplementary Table 1: Baseline participant characteristics by coronary perforation status in patients

Variable	No perforation (n=269,316)	Perforation (n=1,013)
Age (years), ±SD	64.3±14.2	70.2±11.9
Female sex, no. (%)	71,965 (26.7)	358 (35.3)
Smoking status, no. (%)	164,029 (66.1)	591 (64.6)
Year		
2007	19,758 (7)	77 (8)
2008	24,005 (11)	102 (10)
2009	28,603 (11)	96 (9)
2010	34,109 (13)	126 (12)
2011	36,699 (14)	142 (14)
2012	39,448 (15)	132 (13)
2013	42,039 (16)	150 (15)
2014	44,655 (17)	188 (19)
BMI (kg/m2), ±SD	28.0±5.2	27.2±5.1
Hypertension, no. (%)	129,375 (50.6)	564 (58.8)
Diabetes, no. (%)	48,317 (18.4)	169 (17.2)
Previous MI, no. (%)	65,093 (24.8)	288 (30.2)
Previous stroke, no. (%)	11,038 (4.3)	64 (6.6)
Peripheral vascular disease, no. (%)	12,022 (4.7)	80 (8.3)
Q wave on ECG, no. (%)	41,720 (16.7)	192 (20.20
Renal disease, no. (%)	7,272 (2.8)	47 (5.0)
Creatinine (μmol/L), ±SD	94.5±58.7	101.1±77.6
Previous PCI, no. (%)	42,901 (16.2)	179 (18.2)
Previous CABG, no. (%)	17,668 (6.7)	105 (10.6)
EF <30%, no. (%)	9,496 (7.3)	65 (10.8)
Cardiogenic shock, no. (%)	8,639 (3.3)	58 (5.8)
Recent thrombolysis, no. (%)	16,925 (6.7)	46 (4.9)
ST elevation presentation, no. (%)	90,484 (34.1)	299 (30.2)
Antiplatelet therapy, no. (%)		
Clopidogrel	224,900 (83.5)	851 (84.0)
Prasugrel	18,961 (7.0)	56 (5.5)
Ticagrelor	25,457 (9.5)	106 (10.5)
Chronic anticoagulation, no. (%)	2,154 (0.8)	14 (1.4)
No. vessels diseased at baseline, ±SD	1.645±0.70	1.68±0.83

Supplementary Table 2: Procedural variables by coronary perforation status in patients undergoing ACS-PCI in England and Wales 2007-2014

Variable	No perforation (n=269,316)	Perforation (n=1,013)
Radial access, no. (%)	154,896 (58.2)	513 (51.4)
Dual arterial access, no. (%)	9,801 (3.7)	92 (9.2)
No. vessels attempted, ±SD	1.21±0.49	1.35±0.66
No. lesions attempted, ±SD	1.36±0.67	1.56±0.88
In-stent restenosis attempted, no. (%)	10,847 (4.1)	41 (4.0)
CTO attempted, no. (%)	10,922 (4.2)	132 (13.3)
Vessel attempted, no. (%)		
Vein graft	8,703 (3.3)	62 (6.2)
Left main	9,367 (3.5)	95 (9.4)
LAD	123,857 (46.3)	465 (46.2)
Circumflex	64,460 (24.1)	237 (23.5)
Right coronary	99,677 (37.2)	406 (40.3)
Trainee first operator, no. (%)	74,220 (29.0)	214 (21.9)
Intra-coronary imaging, no. (%)	11,716 (5.0)	80 (9.0)
Thrombus aspiration, no. (%)	40,208 (15.9)	129 (13.5)
Distal embolic protection, no. (%)	1,983 (0.8)	12 (1.2)
Rotational atherectomy, no. (%)	3,380 (1.6)	57 (7.0)
Laser atherectomy, no. (%)	377 (0.2)	7 (0.9)
Penetration catheter, no. (%)	1,246 (0.6)	8 (1.0)
Micro-catheter, no. (%)	1,188 (0.6)	21 (2.6)
Crossboss+/-Stingray balloon, no. (%)	91 (0.04)	0 (0)
Bivalirudin, no. (%)	15,366 (5.9)	54 (5.1)
Glycoprotein inhibitor, no. (%)	81,637 (30.3)	270 (26.7)
No. stents used, ±SD	1.48±0.94	2.03±1.57
Largest stent (mm), ±SD	3.34±0.6	3.39±0.8
Longest stent (mm), ±SD	25.0±12.8	32.0±18.6

Supplementary Table 3: Propensity score matching evaluating the association between antiplatelet/glycoprotein IIb/IIIa inhibitor and coronary perforation in patients undergoing ACS-PCI in England and Wales 2007-2014

Variable	**Coefficient (95% CI)**	**p-value**
GPI vs no GPI	-0.0007 (-0.016 to 0.0001)	0.088
Prasugrel vs clopidogrel	-0.0016 (-0.0027 to -0.0004)	0.007
Ticagrelor vs clopidogrel	0.0001 (-0.0016 to 0.0019)	0.89
Prasugrel vs ticagrelor	-0.0016 (-0.0030 to -0.0002)	0.022

Supplementary Table 4: Crude outcomes by coronary perforation status in patients undergoing ACS-PCI in England and Wales 2007-2014

Variable	No perforation (n=269,316)	Perforation (n=1,013)
Immediate procedural outcomes		
No successful lesion, no. (%)	8,639 (3.1)	163 (6.4)
Number of successful lesions, ±SD	1.30±0.67	1.27±0.96
No. residual diseased vessels, ±SD	0.41±0.74	0.75±0.91
Shock induced by procedure, no. (%)	774 (0.3)	57 (6.3)
Tamponade, no. (%)	0 (0)	276 (29.6)
Intra-procedural DC cardioversion, no. (%)	1,558 (0.6)	19 (1.9)
Intra-procedural heart block, no. (%)	818 (0.3)	26 (2.6)
Emergency cardiac surgery, no. (%)	141 (0.05)	23 (2.5)
Coronary dissection, no. (%)	4,386 (1.6)	111 (110)
Major side-branch loss, no. (%)	1,995 (0.7)	40 (4.0)
Slow flow, no. (%)	4,420 (1.6)	35 (3.5)
All coronary complications, no. (%)	14,461 (5.4)	415 (41.1)
Access site complication, no. (%)	2,013 (0.8)	40 (4.1)
Clinical outcomes		
In-hospital repeat procedure, no. (%)	1,669 (0.6)	34 (3.6)
Transfusion, no. (%)	829 (0.3)	64 (6.8)
Gastro-intestinal bleed, no. (%)	1,150 (0.4)	23 (0.5)
In-hospital major bleed, no. (%)	2,464 (0.9)	86 (9.4)
Peri-procedural MI, no. (%)	1,057 (0.4	25 (2.7)
Acute kidney injury, no. (%)	449 (0.2)	9 (1.0)
Peri-procedural CVA, no. (%)	451 (0.2)	2 (0.2)
Length of stay (days), ±SD	2.7±7.2	4.9±7.6
In-hospital death, no. (%)	5,797 (2.2)	147 (14.9)
In-hospital MACCE, no. (%)	7,203 (2.7)	186 (19.8)
Mortality at 30 days, no. (%)	7,250 (3.1)	159 (18.2)
Mortality at 1 year, no. (%)	15,027 (7.0)	200 (22.9)

Supplementary Table 5: Multivariable independent predictors of 30-day mortality during ACS-PCI in England and Wales 2007-2014

Variable	**Odds ratio**	**[95% CI]**	**p-value**
Age (per year)	1.05	[1.02-1.08]	<0.001
Cardiogenic shock on presentation	6.00	[2.50-14.42]	<0.001
Ventilation on presentation	10.57	[2.03-54.91]	0.005
Any GPI	1.58	[0.86-2.92]	0.143
Renal disease	3.05	[1.06-8.79]	0.039