Stroke Following Percutaneous Coronary Intervention: Type-specific incidence, outcomes and determinants seen by the British Cardiovascular Intervention Society 2007-2012

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Abstract

Aims: This study aims to evaluate temporal changes in stroke complications and their association with mortality and MACE outcomes in a national cohort of patients undergoing percutaneous coronary interventions (PCI) in England and Wales.

Methods and Results: 426,046 patients who underwent PCI in England and Wales between 2007 and 2012 in the British Cardiovascular Intervention Society (BCIS) database were analyzed. Statistical analyses were performed evaluating the rates of stroke complications according to year of PCI and multiple logistic regressions were used to evaluate the odds of 30-day mortality and in-hospital major adverse cardiovascular events (MACE; a composite of in-hospital mortality, myocardial infarction or re-infarction and revascularization) with stroke complications. 436 patients (0.1%) sustained an ischaemic stroke/TIA complication and 107 patients (0.03%) sustained a haemorrhagic stroke complication. Ischaemic stroke/TIA complications increased non-linearly from 0.67(0.47-0.87) to 1.14(0.94-1.34) per 1000 patients between 2007 and 2012 (P=0.006) whilst haemorrhagic stroke rates decreased non-linearly from 0.29(0.19-0.39) to 0.15(0.05-0.25) per 1000 patients in 2012 (P=0.009). Following adjustment for baseline clinical and procedural demographics, ischaemic stroke was independently associated with both 30-day mortality (OR 4.92, 3.06-7.92) and in-hospital MACE (OR 3.11, 1.83-5.27). An even greater impact on prognosis was observed with haemorrhagic complications (30-day mortality: OR 13.87, 6.37-30.21), in-hospital MACE (OR 13.50, 6.30-28.92).

Conclusions: Incident ischemic stroke complications have increased over time, whilst haemorrhagic stroke complications have decreased, driven through changes in clinical, procedural, drug-treatment and demographic factors. Both ischemic and haemorrhagic strokes are rare but devastating complications with high 30-day mortality and in-hospital MACE rates.

Introduction

Both major adverse cardiovascular events (MACE) and mortality following percutaneous coronary intervention (PCI) have declined over the past 25-years despite rising patient age, increases in co-morbidity and a shift in indication from mostly elective to more emergent, higher risk interventions[1]. Although MACE have declined over time, the changes in patterns of stroke following PCI have not been fully described, particularly from a national perspective. Incident stroke rates have been reported between 0.1-0.6% in single-centre and other national registry data[2-7].

Stroke as a complication of PCI is associated with high in-hospital mortality rates[6-8] and potentially causes significant and devastating life changing disabilities in surviving patients[5,9,10]. The stroke complications of PCI can be ischaemic or haemorrhagic[10]. Guide catheter manipulation within the aortic arch or use of circulatory support devices during PCI can cause embolization of atherosclerotic material from the aorta leading to ischaemic stroke complications[11] and an ageing population undergoing PCI with high prevalences of co-morbid conditions further increases the risk of stroke complications during PCI[6]. In addition, use of potent antiplatelet and anti-coagulant therapies during PCI increases the risk of haemorrhagic stroke in such patients.

Previous large-scale studies (e.g. from the Euro Heart Survey Percutaneous Coronary Interventions survey[7] and the National Cardiovascular Data Registry (NCDR) from North America[6] have studied the incidence, major determinants and outcomes of stroke following PCI. These studies, however, have not differentiated between ischaemic and haemorrhagic mechanisms, nor have they looked at temporal changes, which is especially important given the changing indications for PCI and its application to an older population. Whilst more detailed study from single centres is enlightening[1,4] these studies may not be generalizable as the observations relate to a specific case-mix and local procedural practice.

We have therefore studied the temporal changes in haemorrhagic and ischaemic stroke in an unselected cohort of patients undergoing PCI in England and Wales through analysis of the British Cardiovascular Intervention Society (BCIS) database. We report the clinical and procedural predictors of both types of stroke and their associated mortality and MACE outcomes.

Methods

The British Cardiovascular Intervention Society Database

The British Cardiovascular Intervention Society (BCIS) collects data on all PCI procedures in the UK. The data collection is coordinated by the National Institute of Cardiovascular Outcomes Research (www.ucl.ac.uk/nicor) via the Central Cardiac Audit Database. In 2011, this dataset collected information on 99% of all PCI procedures performed in National Health Service Hospitals in England and Wales.

The BCIS-NICOR database contains a total of 113 variables, which includes information on clinical variables, procedural parameters and patient outcomes. Mortality tracking is undertaken by the Medical Research Information Service (MRIS) using patients' NHS number that provides a unique identifier for any person registered with the NHS in England and Wales. Mortality tracking was not possible in this study for patients from Scotland or Northern Ireland.

Study definitions

We analysed all patients who underwent PCI in the UK between 1 January 2007 and 31 December 2012. Patients were classified into three groups: i) patients with no in-hospital stroke complications, ii) ischaemic stroke or transient ischaemic attack (TIA) in-hospital complication and iii) haemorrhagic stroke complication. The main outcomes that were examined were 30-day mortality and in-hospital major adverse cardiovascular events. Major adverse cardiovascular events were defined as the composite of in-hospital mortality, myocardial infarction or re-infarction and revascularization (emergency coronary artery bypass graft or re-intervention PCI).

Additional data were collected on baseline variables including year of procedure, age, gender, smoking status, comorbidities (diabetes, hypertension, hyperlipidaemia, previous myocardial infarction, previous stroke, peripheral vascular disease, chronic renal disease and previous valve disease), previous PCI, previous coronary artery bypass graft, access site, cardiogenic shock, use of circulatory support, thrombus aspiration, use of ventilatory support, revascularization of the left main stem, indication/diagnosis (stable angina, NSTEMI, STEMI) and medications received (any glycoprotein IIb/IIIa inhibitor, aspirin, clopidogrel, prasugrel, ticagrelor, ticlopidine and warfarin use).

Statistical analysis

Statistical analyses were performed using Stata/MP version 13 (Stata Corp, TX, USA) and StatsDirect version 3 (StatsDirect Ltd, UK).

Summary statistics were expressed as means and standard deviations for continuous variables, and percentages for categorical variables. Comparisons of means were made using t-tests and one-way analyses of variance, with appropriate consideration of multiple testing for pairwise contrasts of the three main groups. Proportions were compared using Fisher's method for fourfold tables and chi-square (with simulated exact P-values) linear trend tests for ordinal series. We excluded patients with missing values for age, mortality at 30 days, MACE and stroke complications. A flow diagram graphically describes how the final cohort was derived (Figure 1).

We present descriptive statistics of baseline variables by complication group in Table 1. We graphically examined the rates of ischaemic stroke or TIA and haemorrhagic stroke over time (Figure 2). Simple logistic regressions were used to investigate the effect of each baseline variable as a potential predictor of ischaemic stroke or TIA and haemorrhagic stroke. Multiple logistic regressions, in which all baseline variables and year of PCI were included in the two models, were used to identify predictors of: i) ischaemic stroke or TIA; and ii) haemorrhagic stroke.

The primary outcomes were 30-day mortality and in-hospital MACE. Multiple logistic regressions were used to investigate the effect of each neurological complication on 30-day mortality and in-hospital MACE rates, using both unadjusted and adjusted for baseline variables models. The final adjusted models were controlled for all collected baseline variables and year of PCI. Chained equations multiple imputations (using mi impute chained in Stata) were used to generate 10 complete datasets with imputed data for missing baseline variables. Additional sensitivity analyses were ran in which we tried to better control for covariates. Under a similar multiple imputation setting, we calculated the propensity scores for membership on each group in the comparisons we investigated, using all available covariates. Using the aggregate patient propensity score across all 10 multiple imputation datasets, we then matched each 'case' (e.g. TIA only) to up to 10 'controls' (e.g. no TIA) with scores within 10^{-5}.

Cases with missing data that were excluded from the analyses were compared to cases that were included in the final analysis, for baseline variables and outcomes (when available) (Supplementary Table 1). Results are presented as the main effect with 95% confidence interval unless otherwise stated.

Results

A total of 438,400 patients underwent PCI in England and Wales and 426,297 patients were included in the analysis after exclusion of participants with missing values for mortality at 30 days, and stroke outcomes. Figure 1 shows the process of patient inclusion. A comparison of patient characteristics for included participants and excluded participants is shown in Supplementary Table 1. Supplementary Table 2 and 3 shows missing data for each variable and by year of procedure. Many of the characteristics compared showed statistically significant differences between those included in the study and the 12,103 patients excluded for the analysis although there were no material differences in stroke risk factors such as age, previous CVA, diabetes, hypertension and 30 day mortality outcomes were similar.

A total of 543 (0.13%) patients experienced an in-patient stroke complication following PCI of which 436 patients (0.1%) sustained an ischaemic stroke complication and 107 patients (0.03%) sustained a haemorrhagic stroke complication. The rates of ischaemic stroke/TIA and haemorrhagic stroke according to year of PCI are shown in Figure 2. Ischaemic stroke/TIA complications increased non-linearly from 0.67(0.47-0.87) to 0.114(0.094-0.134) per 1000 patients between 2007 and 2012 (P=0.006) whilst haemorrhagic stroke rates decreased non-linearly from 0.29(0.19-0.39) to 0.15(0.05-0.25) per 1000 patients in 2012 (P=0.009) (Supplementary table 4). Interestingly TIA rates remained similar over the study period from 0.34 (0.24-0.44) per 1000 patients in 2007 to 0.39 (0.29-0.49) in 2012, whilst ischaemic stroke rates increased from 0.33 (0.23-0.43) per 1000 patients in 2007 to 0.75 (0.55-0.95) in 2012.

Clinical and procedural demographics are presented in Table 1. Patients who experienced ischaemic stroke complications or TIA following PCI were older, more likely to have a previous history of stroke, more likely to be female, have valvular heart disease and were more likely to present as non-elective cases compared to those patients that did not experience cerebrovascular complications. Similarly, patients with haemorrhagic stroke complications were more likely to be older, female, undergo PCI for non-elective indications and be more haemodynamically unstable as evidenced by the increased rates of cardiogenic shock and circulatory support in this group. Furthermore, Patients with haemorrhagic strokes were more likely to have been treated with warfarin, thrombolysis and glycoprotein IIb/III inhibitors.

30-day mortality rate was 8,597/425,503 (2.0%) in the control group, 70/436 (16%) in the group of patients who experienced an ischaemic stroke /TIA and 51/107 (48%) for the cohort of patients who experienced a haemorrhagic stroke complication. Similar rates of MACE were observed across the groups. Supplementary table 5 presents crude mortality and MACE rates for the stroke / TIA cohort separate into separate ischaemic stroke and TIA groups. 30-day mortality was 55/261 (21%) in patients who sustained ischemic stroke complications and 15/175 (9%) in patients with TIA complications.

Simple and multiple logistic regression, (in the latter adjusting for all baseline clinical and procedural demographics) was performed to identify predictors of both ischaemic stroke/TIA and haemorrhagic stroke complications (Tables 2 and 3). After adjustments for baseline variables, factors independently associated with increased odds of ischaemic stroke/TIA included age, previous stroke, female gender, valvular heart disease, receipt of circulatory support, thrombus aspiration and diagnosis of NSTEMI and STEMI (Table 3). For haemorrhagic stroke complications, independent predictors following adjustment for baseline covariates included age, valvular heart disease, diagnosis of NSTEMI or STEMI, receipt of thrombolysis and warfarin use (Table 3).

In order to study how changes in clinical and procedural demographics have contributed to the changes in the incidence of both ischemic (increase) and haemorrhagic (decrease) stroke rates over time, we have presented how predictors of both stroke types have varied over time (Table 4). The average age of the cohort, use of circulatory support devices, prevalence of patients with valvular heart disease or a previous history of stroke, and procedures undertaken for STEMI indications have all increased over time, which would contribute to the increased incidence of ischaemic stroke event rates observed. In contrast, whilst the prevalence of warfarin use and valvular heart disease, average age and procedures undertaken for STEMI indications have increased over time, which would contribute to an increased incidence of haemorrhagic stroke, there has been a major decrease in thrombolysis (from 9.26% in 2007 to 1.16% in 2012; $P<0.001$) that would tend to reduce incident haemorrhagic stroke complications.

We investigated the association between stroke complications and adverse outcomes (Table 5). An ischaemic stroke complication (or TIA) was associated with a 9-fold increased odds of 30-day mortality (OR 9.27, 7.18-11.99) and an 8-fold

increased odds of in-hospital MACE (OR 8.34, 6.48-10.73). Following adjustment for baseline clinical and procedural demographics, ischaemic stroke remained independently associated with both 30-day mortality (OR 4.94, 3.07-7.93) and in-hospital MACE (OR 3.13, 1.84-5.30). Supplementary Table 6 separates the prognostic impact of TIA and ischaemic stroke complications on 30-day mortality and in-hospital MACE and demonstrates that both Stroke and TIA complications independently predicted MACE (OR 3.16 95% 1.65-6.07 and OR 3.07 95% CI 1.26-7.48) and 30-day mortality (OR 4.79 95 % CI 2.68-8.57 and OR 5.24 95% CI 2.32-11.81).

An even greater impact on prognosis was observed with haemorrhagic complications, with up to a 40-fold increase in odds of 30-day mortality (OR 44.2, 30.2-64.6) and MACE (OR 37.8, 25.82-55.20). Even after adjustment for baseline covariates, this relationship persisted (30-day mortality: OR 13.83, 6.35-30.12), in-hospital MACE (OR 13.19, 6.15-28.30).

In order to reduce the influence of unmeasured confounders on outcomes, a propensity score matched cohort was generated (propensity score difference below 10^{-5}). The logistic regression results with multiple imputation in the propensity-matched cohort are shown in Table 6. Both ischaemic stroke / TIA and haemorrhagic stroke were associated with increased odds of 30-day mortality (OR 2.66 95% CI 1.97-3.60 and OR 4.08 95% CI 2.61-6.38 respectively) and in-hospital MACE (OR 2.54 95% CI 1.88-3.42 and OR 3.83 95% CI 2.45-5.98 respectively). When ischaemic stroke and TIA were studied separately, the increased odds of 30-day mortality remained significant for both an ischaemic stroke (OR 2.79 95% CI 1.96-3.97; P<0.001) and TIA (OR 1.85 95% CI 1.02-3.35; P=0.042). For completeness, we present the propensity scores within each group in Supplementary Table 7.

Discussion

In one of the largest population-based case-cohort analyses published to date, we have shown that the incidence of ischemic stroke complications in contemporary PCI practice is 3-fold greater than that of haemorrhagic stroke. Ischaemic stroke complications have increased in incidence over time, whilst haemorrhagic stroke complications have decreased, driven through temporal changes in clinical, procedural, drug-treatment and demographic factors. Furthermore, we demonstrate that both ischemic and haemorrhagic strokes are rare but have devastating complications with high 30-day mortality and in-hospital MACE rates, with ischaemic stroke independently associated with a 5-fold increased odds and haemorrhagic stroke with a 14-fold increase in odds of 30-day mortality post PCI.

Our data show an incident in-hospital stroke rate of 0.13% in our unselected national cohort of patients undergoing PCI, with a 3-fold greater incidence of ischaemic strokes compared to haemorrhagic strokes. Studies such as the SYNTAX study have reported incident stroke rates of 0.2% at 30-days[12] with the ACUITY trial reporting rates of up to 0.3%[13], whilst national registries such as the NCDR and international registries such as the EuroHeart survey have reported stroke rates between 0.2 and 0.4% respectively[6,7]. Other, single centre, registry studies have reported rates of between 0.15 - 0.4%[3,4]. Incident stroke rates will depend on the clinical characteristics of the cohort studied, with a 2-fold greater incidence reported in patients undergoing PCI for ACS indications compared to the elective setting in the EuroHeart survey[7].

To the best of our knowledge, our analysis is the first to systematically study haemorrhagic and ischemic stroke complications separately following PCI from a large scale national perspective, with such data either not being available for analysis in previous reports derived from the NCDR[6] or not presented in the EuroHeart survey[7]. In a single centre study of Hoffman et al undertaken at the Mayo clinic that reported incident stroke complications of 0.37%, 90% of all stroke complications were ischemic in origin whereas 7% were reported as haemorrhagic strokes[4], although predictors, outcomes and changes in incidence over time were not studied separately for each sub-type of stroke.

We have observed that incident stroke rates have increased over a 6-year timeframe in England and Wales, which has been driven by an increase in incident

ischemic stroke complications, whereas haemorrhagic stroke rates have decreased over a similar time frame. Whilst changes in incident stroke have not been previously reported from a national perspective, single centre studies report varying results with both significant and non-significant decreases[14] and non-significant increases in stroke rates over time[3]. In the Swedish heart intensive care admission registry[15], haemorrhagic strokes were reported to decrease by over 50% over a 10-year period in acute myocardial infarction, driven largely through changes in thrombolysis practice, although in those patients who underwent primary PCI, rates of haemorrhagic strokes remained relatively stable over time.

We have identified a number of independent predictors of ischaemic stroke complications such as female gender, increasing age, prevalent valvular heart disease, a previous history of stroke, use of circulatory support devices and PCI in the setting of both NSTEMI and STEMI. Similarly, previous analyses have also identified female gender[4,6,7], previous stroke history[3,4], age[4,6,7,13,14], circulatory support devices[6,14], thrombus containing lesions[3] and PCI for ACS indications[4,6,14] as independent predictors of stroke complications. Our analysis suggests that the presence of valvular heart disease is amongst the strongest predictors of ischaemic stroke complications. Similarly, the smaller euro heart registry consisting of 46,888 patients has documented that prevalent valvular heart disease is associated with a 2-fold increase in stroke risk although this did not reach statistical significance[7]. The BCIS dataset does not differentiate between native valvular heart disease and its severity, and prosthetic valves that might increase risk of thrombotic embolisation and ischaemic stroke complications, particularly if anti-coagulants have been discontinued for the PCI procedure. In addition, valvular heart disease such as aortic stenosis[16] and mitral valve disease[17] are well-described independent predictors of stroke risk. Finally the presence of valvular heart disease may be a surrogate for prevalent atrial fibrillation that is unrecorded in the BCIS dataset that would in itself increase stroke risk.

Our analysis suggests that the observed increase in incident ischemic stroke complications over time may relate to temporal changes in patient demographics and PCI practice. The average age of the cohort has increased over time, along with the prevalence of valvular heart disease, history of stroke, ACS indications for PCI and increases in circulatory support device use over time that would all contribute to the increases in stroke rates reported.

We identify both a number of shared risk factors such as age, ACS indications for PCI and valvular heart disease as important independent predictors of haemorrhagic stroke complications as well as additional risk factors such as warfarin use and thrombolysis that are independent predictors for only haemorrhagic strokes. We also identify GPIIb/IIIa and haemodynamic instability such as cardiogenic shock presentation, receipt of ventilatory or circulatory support as uni-variate predictors of haemorrhagic stroke. Whilst age, thrombolysis and warfarin use are recognised risk factors for haemorrhagic strokes, the mechanism through which the presence of valvular heart disease independently predicts stroke is not clear. Valvular heart disease may be a surrogate for anticoagulant use, that may not have been fully captured in the BCIS dataset, both from the perspective of anti-coagulant for thromboprophylaxis for atrial fibrillation (that is associated with prevalent valvular heart disease) and for prosthetic heart valves. Changes in both platelet physiology [18] and coagulation pathways[19] are well documented in cardiogenic shock that might contribute to the increased haemorrhagic complications observed in cardiogenic shock on univariate analysis[20].

It is of interest that we have identified ACS indications for PCI as independent predictors for both ischemic and haemorrhagic stroke complications, analogous to the observation that both STEMI and NSTEMI are strong independent predictors of both stent thrombosis[21] and major bleeding complications[22] during PCI which may relate to increased thrombus burden in lesions treated for ACS indications, higher anti-platelet reactivity hence the requirement for more aggressive antiplatelet and anti-coagulant regime use. Similarly, prevalent valvular heart disease is a strong independent predictor of both ischaemic and haemorrhagic stroke complications. As described, patients with prevalent valvular heart disease within the BCIS database are a heterogeneous cohort of patients consisting of patients with native valvular heart disease of varying severity and patients with prosthetic heart valves. These patients with prevalent valvular heart disease will have a significant prevalence of atrial fibrillation that is not captured in the BCIS dataset and a significant proportion of such patients will be anti-coagulated both for thromboprophylaxis against AF as well as for prosthetic heart valves. This heterogeneous cohort of patients will have important risk factors for both haemorrhagic and ischaemic stroke complications hence the importance of valvular heart disease as a predictor of both haemorrhagic and ischemic stroke complications.

It is likely that competing risks contribute overall to the observed decline in haemorrhagic stroke rates over time. Some of the independent predictors of haemorrhagic stroke have increased in prevalence over time such as warfarin use, valvular heart disease, STEMI PCI and average age which would tend to favour an increase in haemorrhagic strokes whilst other important independent predictors such as thrombolysis have declined over time, which reflect changes in PCI practice particularly with a move from rescue PCI, facilitated PCI or PCI following successful thrombolysis in STEMI towards primary PCI more recently. Indeed, in the Swedish heart intensive care admission registry[15], haemorrhagic strokes were reported to decrease by over 50% over a 10-year period in acute myocardial infarction, driven largely through changes in thrombolysis practice.

Our analysis suggests that stroke complications independently predict adverse mortality and MACE outcomes, and that haemorrhagic stroke complications are independently associated with a 10–fold increased odds of 30-day mortality, whilst ischemic stroke complications increase this 4-fold. Whilst most previous studies have not reported the prognostic impact of stroke complications according to whether the aetiology is ischaemic or haemorrhagic, stroke was associated with a 12-fold unadjusted increase in in-hospital mortality and a 10-fold increase in MACE in the EuroHeart registry[7]. Similarly data derived from the ACUITY trial has reported unadjusted 8-fold increases in 30 day mortality and 2.4 fold increases in MACE events following stroke[13]. In a patient-level pooled analysis of the 7 ISAR trials, intracranial bleeding was associated with a 22-fold unadjusted increase risk in 1-year mortality, although this data was based on a total of 9 intra-cranial bleeding events[23]. These observations are in keeping with our reported unadjusted rates of 9-fold increase in 30-day mortality for ischemic strokes and 44-fold increase for haemorrhagic strokes. Indeed in an analysis undertaken at the Mayo clinic in which cause of death was studied in patients undergoing PCI over a 17-year period, stroke events accounted for 6% of all mortalities during this period of time[24] whilst another single centre study has suggested that neurological complications contribute to 15% of mortalities post PCI[25]. We have also attempted to separate the prognostic impact of ischaemic strokes and TIA and shown that both TIA and stroke are independently associated with increased odds of 30-day mortality and MACE in our main analysis and propensity score matching. Interestingly, when the impact of stroke versus TIA on one-year all-cause mortality was separately considered in an analysis of the Acuity

trial, mortality was significantly increased after the occurrence of stroke (HR 4.16, 95% CI [2.13, 8.13], p<0.001) but not after TIA (HR 1.52, 95% CI [0.21, 10.83], p=0.68) although this may have been limited by the statistical power of this analysis as evidenced by the wide confidence intervals.[13] Finally, whilst we have attempted to adjust for differences in baseline covariates between patients who sustained stroke complications and those who did not, and attempted to reduce the influence of the potential confounders through the use of propensity score matching, our association between stroke complications and increased odds of mortality and MACE outcomes does not infer a causal relationship, but maybe driven by unmeasured confounders or unrecorded measures of frailty.

Whilst the absolute 30-day mortality rates for ischaemic and haemorrhagic strokes of 16 and 48% respectively are striking, even those patients that survive would have significant life changing disabilities, for example in the SYNTAX study, close to 60% of patients who experienced a stroke complication and survived were left with residual neurological deficits post hospital discharge[12]. Similarly, in the single centre analysis of Dukkipati et al[14], 70% of patients who survived the stroke were left with significant neurological deficit with skilled home care needed in 26% of patients, nursing home or assisted living in 9%, and inpatient rehabilitation in 22%. Our group has previously reported in an analysis of over 3000 community patients admitted with stroke in England, similar 30-day mortality rates to those reported here, with 18% 30-day mortality for ischaemic strokes and 42% mortality for haemorrhagic strokes[26], suggesting that the adverse outcomes associated with stroke complications following PCI are similar to those observed in the community. Whilst community stroke registries have suggested that haemorrhagic strokes account for around 15% of all strokes in the UK[26-28], haemorrhagic strokes account for 25% in our analysis, which may relate to the potent drug therapies used in PCI that predispose to haemorrhagic complications.

Our study has several strengths. The BCIS dataset includes >95% of all PCI procedures performed in the United Kingdom which therefore reflects a national, real-world experience that includes high-risk patients encountered in daily interventional practice who are often excluded from randomized controlled trials. In our current analysis, we have studied neurovascular complications in over 400,000 patients and as such this analysis represents the one of the largest analyses of changes in incident neurovascular complications over time and due to its size is able to: capture relatively

rare complications of PCI; and for the first time from a national perspective, systematically study changes, predictors and outcomes of both ischaemic and haemorrhagic stroke complications.

There are some limitations in this study, which are worth highlighting. Our dataset does not capture the timing of the stroke complications. Furthermore, the BCIS dataset does not provide information regarding the neurological deficit sustained following a stroke. In the study of Dukkipati et al. the 3 most common neurological manifestations were motor (35%), speech (33%) and mental state changes (32%) [14] whilst in the study of Hoffman the most frequently occurring clinical features were limb motor weakness (49%), speech impairment (39%), visual disturbance (20%), and facial droop (18%) and unresponsiveness was present in 12% [4]. Similar to previous large national and multi-national studies, BCIS does not record prevalent atrial fibrillation (AF), which is a similar limitation encountered in both analysis derived from the EuroHeart Survey[7] and NCDR dataset[6]. Nevertheless, whilst AF contributes to about 15% of ischaemic strokes and is hence one of the most important predictors stroke in the community setting[29,30], the role of AF as a risk factor for stroke following PCI has not been widely studied. Our analysis suggests that valvular heart disease is one of the most powerful predictors of ischemic stroke events that may be a surrogate marker for incident AF. Interestingly in one analysis where prevalent AF data was recorded, whilst AF was more common in patients who sustained a stroke complication following PCI, prevalent AF did not independently increase risk of stroke in this setting [3].

Thirdly, diagnosis of stroke is self-reported by individual operators with no external validation hence there is the potential for under-reporting of neurological events, although our reported incident stroke rates are similar in magnitude to those reported in the national NCDR[6] and the SCAAR[31] datasets derived from USA and Sweden respectively.

Finally, our analysis reports in-hospital stroke events that may represent periods of only a few hours of time for day case procedures or a few days for other inpatient cases. Previous findings from a single centre data suggest that 60% of strokes occur within 24 hours and 20 % between 24-48 hours with the remaining events occurring after 48 hours[14] that may explain differences in reported stroke rates in our analysis and those reported in randomised trials that report stroke events upto 30-days post index procedure[12,13].

In conclusion, we have shown that the incidence of ischemic stroke complications in contemporary PCI practice is 3-fold greater than that of haemorrhagic stroke, with ischemic stroke complications increasing in incidence over time, whilst haemorrhagic stroke complications have decreased, and that these changes in incident rates have been driven through changes in clinical, procedural, drug-treatment and demographic factors over time. Furthermore, we confirm that both ischemic and haemorrhagic strokes are rare but devastating complications with high 30-day mortality and in-hospital MACE rates.

Contributorship

MAM and PKM conceived the idea. CSK and EK designed the analysis plan and analysed the data. MAM drafted the manuscript with critical inputs from all authors. All authors contributed to the writing of the paper. MAM is the guarantor.

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Figure Legends

Figure 1: Flow chart of participant inclusion

Figure 1: Flow chart of participant inclusion

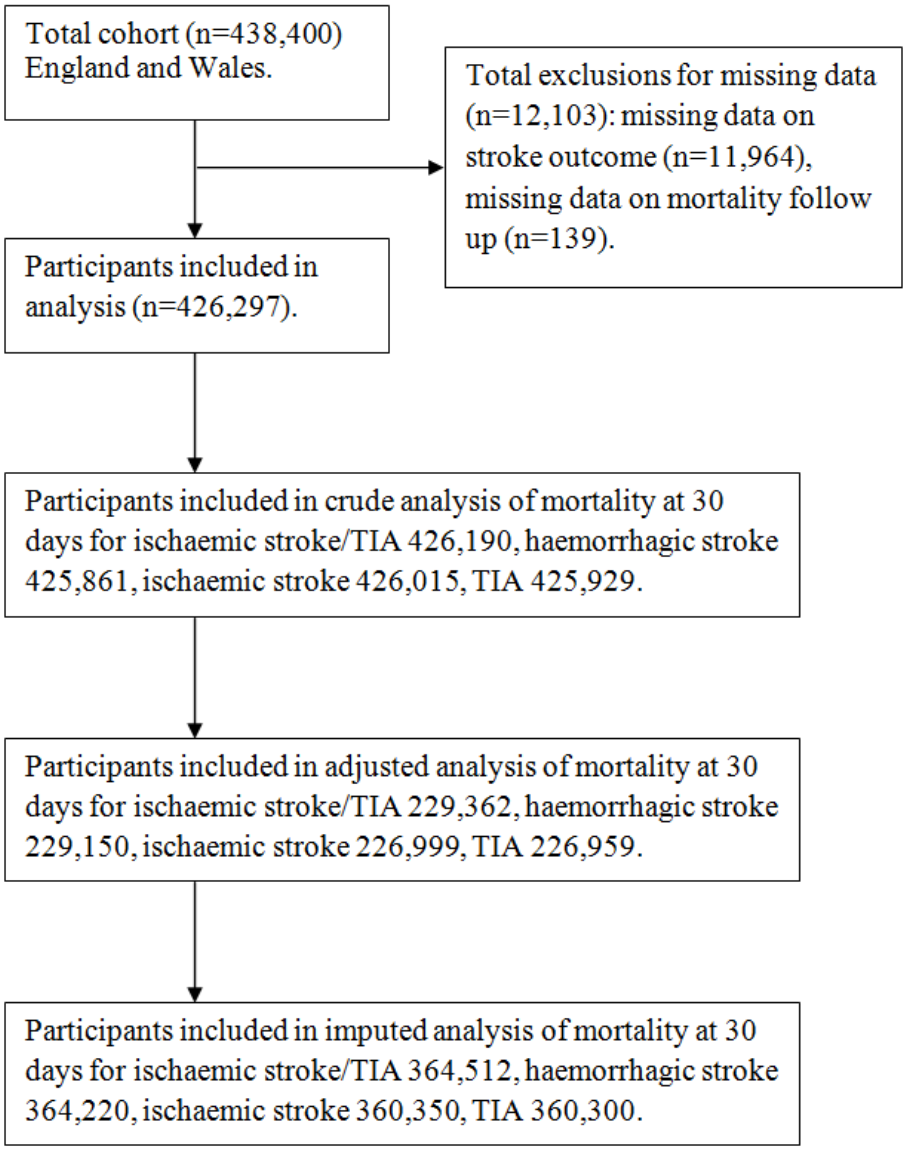
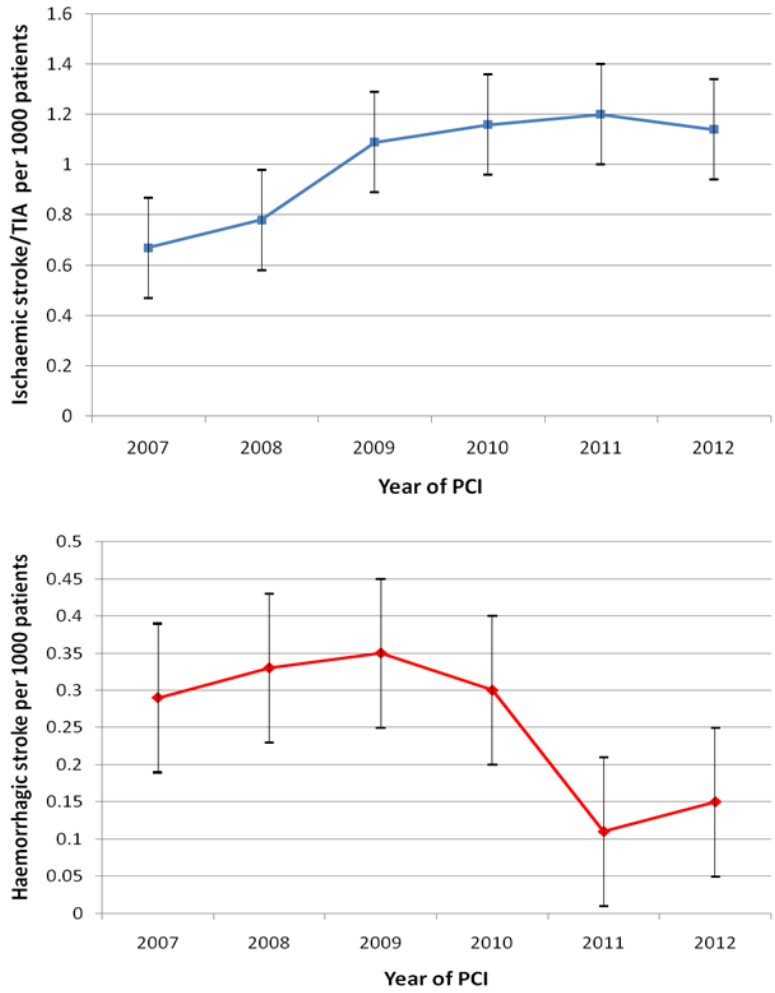


Figure 2: Rates of stroke/transient ischaemic attack and haemorrhagic stroke complications according to year of PCI

Figure 2: Rates of stroke/transient ischaemic attack and haemorrhagic stroke complications according to year of PCI



Caption for Figure 2: Changes in the rates (per 1000 patients) of ischaemic stroke / TIA complications and haemorrhagic stroke complications over time (2007-2012). Error bars represent 95% confidence intervals.

Table 1: Patient characteristics contrasting stroke types with no stroke

Variable	No stroke (n=425,503)	Ischaemic stroke (n=436)	P-value	Haemorrhagic stroke (n=107)	P-value
Age	65 (±12)	71 (±12)	<0.001	69 (±11)	<0.001
Female gender	110,568/424,622 (26%)	157/436 (36%)	<0.001	42/107 (39%)	0.003
Smoking (current or ex smoker)	241,845/373,796 (65%)	247/391 (63%)	0.53	58/94 (62%)	0.59
Diabetes	76,767/406,931 (19%)	81/431 (19%)	1.00	22/104 (21%)	0.53
Hypertension	219,550/415,737 (53%)	238/432 (55%)	0.36	59/106 (56%)	0.63
Hyperlipidaemia	232,720/415,737 (56%)	230/432 (53%)	0.27	51/106 (48%)	0.12
Previous MI	106,856/379,338 (28%)	107/392 (27%)	0.74	28/99 (28%)	1.00
Previous CVA	14,991/415,737 (3.6%)	45/432 (10%)	<0.001	10/106 (9.4%)	0.008
Peripheral vascular disease	19,726/415,737 (4.7%)	36/432 (8.3%)	0.001	10/106 (9.4%)	0.035
Renal disease	10,785/402,954 (2.7%)	12/421 (2.9%)	0.76	5/100 (5.0%)	0.20
Previous valvular heart disease	4,650/425,499 (1.1%)	45/436 (10.3%)	<0.001	34/107 (32%)	<0.001
Previous PCI	90,515/408,153 (22%)	71/432 (16%)	0.004	24/104 (23%)	0.81
Previous CABG	34,333/407,114 (8.4%)	35/425 (8.2%)	1.00	6/103 (5.8%)	0.48
Access site Femoral Radial	 225,748 (56%) 177,149 (44%)	 212 (52%) 199 (48%)	0.073	 76 (77%) 23 (23%)	<0.001
Cardiogenic shock	8,036/397,267 (2.0%)	33/425 (7.7%)	<0.001	19/102 (19%)	<0.001
Use of circulatory support	8,336/395,144 (2.1%)	39/426 (9.2%)	<0.001	18/105 (17%)	<0.001
Thrombus aspiration	45,873/397,263 (12%)	117/421 (28%)	<0.001	25/106 (24%)	0.001
Ventilatory support	4,887/355,239 (1.3%)	21/387 (5.4%)	<0.001	10/97 (10%)	<0.001
Left main stem revascularization	13,138/411,575 (3.2%)	20/431 (4.6%)	0.098	8/106 (7.5%)	0.021
Diagnosis Stable angina NSTEMI STEMI	 172,553 (41%) 157,582 (38%) 88,815 (21%)	 84 (19%) 153 (35%) 197 (45%)	<0.001	 17 (16%) 30 (28%) 60 (56%)	<0.001
Glycoprotein	88,024/372,657	144/400 (36%)	<0.001	45/102 (44%)	<0.001

IIb/IIIa	(24%)				
Aspirin	329,975/394,968 (84%)	354/414 (86%)	0.32	82/101 (81%)	0.50
Clopidogrel	304,885/394,968 (77%)	317/414 (77%)	0.77	81/101 (80%)	0.55
Prasugrel	13,465/394,968 (3.4%)	25/414 (6.0%)	0.006	2/101 (2.0%)	0.59
Ticagrelor	2,782/394,968 (0.7%)	1/414 (0.2%)	0.38	0/101 (0%)	1.00
Ticlopidine	1,362/394,968 (0.3%)	2/414 (0.5%)	0.66	0/101 (0%)	1.00
Warfarin	3,779/394,968 (1.0%)	8/414 (1.9%)	0.067	3/101 (3.0%)	0.074
Thrombolysis	18,680/385,407 (4.8%)	18/409 (4.4%)	0.68	27/106 (25%)	<0.001
30-day mortality	8,597/425,503 (2.0%)	70/436 (16%)	<0.001	51/107 (48%)	<0.001
MACE	10,022/425,503 (2.4%)	73/436 (17%)	<0.001	51/107 (48%)	<0.001

Table 2: Univariate baseline predictors of ischaemic stroke/transient ischaemic attack and haemorrhagic stroke

Variable	Ischaemic stroke or transient ischaemic attack		Haemorrhagic stroke	
	Odds ratio (95% CI)	P-value	Odds ratio (95% CI)	P-value
Age	1.05 (1.04-1.06)	<0.001	1.03 (1.02-1.05)	<0.001
Male gender	0.63 (0.51-0.76)	<0.001	0.55 (0.37-0.80)	0.002
Current smoker	0.94 (0.76-1.15)	0.527	0.88 (0.58-1.33)	0.544
Diabetes	1.00 (0.78-1.27)	0.970	1.15 (0.72-1.85)	0.551
Hypertension	1.10 (0.91-1.33)	0.342	1.12 (0.76-1.65)	0.557
Hyperlipidaemia	0.90 (0.74-1.08)	0.252	0.73 (0.50-1.07)	0.104
Previous MI	0.96 (0.77-1.20)	0.701	1.01 (0.65-1.56)	0.980
Previous CVA	2.91 (2.13-3.96)	<0.001	2.60 (1.35-4.99)	0.004
Peripheral vascular disease	1.83 (1.30-2.57)	0.001	2.09 (1.09-4.01)	0.027
Renal disease	1.07 (0.60-1.89)	0.825	1.91 (0.78-4.70)	0.157
Previous valvular heart disease	10.42 (7.64-14.20)	<0.001	41.79 (27.79-62.84)	<0.001
Previous PCI	0.69 (0.54-0.89)	0.004	1.05 (0.67-1.66)	0.824
Previous CABG	0.97 (0.69-1.38)	0.883	0.67 (0.29-1.53)	0.344
Radial access	1.20 (0.99-1.45)	0.070	0.39 (0.24-0.61)	<0.001
Cardiogenic shock	4.08 (2.86-5.82)	<0.001	11.05 (6.71-18.21)	<0.001
Use of circulatory support	4.68 (3.36-6.50)	<0.001	9.57 (5.76-15.90)	<0.001
Thrombus aspiration	2.95 (2.38-3.65)	<0.001	2.36 (1.51-3.70)	<0.001
Ventilatory support	4.11 (2.65-6.39)	<0.001	8.21 (4.27-15.81)	<0.001
Left main stem revascularization	1.48 (0.94-2.31)	0.089	2.47 (1.20-5.09)	0.014
Diagnosis		<0.001		

NSTEMI STEMI	1.99 (1.53-2.60) 4.56 (3.53-5.88)		1.93 (1.07-3.50) 6.85 (3.99-11.73)	0.030 <0.001
Glycoprotein IIb/IIIa	1.82 (1.48-2.23)	<0.001	2.55 (1.73-3.77)	<0.001
Aspirin	1.16 (0.88-1.53)	0.282	0.85 (0.52-1.40)	0.523
Clopidogrel	0.97 (0.77-1.21)	0.763	1.20 (0.73-1.95)	0.472
Prasugrel	1.82 (1.21-2.73)	0.004	0.57 (0.14-2.32)	0.434
Ticagrelor	0.34 (0.05-2.43)	0.283	No events	-
Ticlopidine	1.40 (0.35-5.63)	0.633	No events	-
Warfarin	2.04 (1.01-4.11)	0.046	3.17 (1.00-9.99)	0.049
Thrombolysis	0.90 (0.56-1.45)	0.68	6.71 (4.33-10.39)	<0.001
Year	1.11 (1.05-1.17)	<0.001	0.84 (0.75-0.94)	0.003

Table 3: Independent predictors of ischaemic stroke/transient ischaemic attack and haemorrhagic stroke

Significant predictors of ischaemic stroke or transient ischaemic attack (n=238,707)		
Variable	Odds ratio (95% CI)	P-value
Age	1.05 (1.04-1.06)	<0.001
Male gender	0.68 (0.53-0.87)	0.002
Previous stroke	1.88 (1.27-2.78)	0.002
Previous valvular heart disease	4.48 (2.87-7.00)	<0.001
Receipt of circulatory support	1.71 (1.03-2.84)	0.038
Thrombus aspiration	1.64 (1.19-2.27)	0.003
Diagnosis of NSTEMI	1.84 (1.30-2.61)	0.001
Diagnosis of STEMI	2.88 (1.92-4.33)	<0.001
Significant predictors of haemorrhagic stroke (n=225,708)		
Variable	Odds ratio (95% CI)	P-value
Age	1.03 (1.00-1.05)	0.024
Previous valvular heart disease	21.30 (10.73-42.28)	<0.001
Diagnosis of NSTEMI	3.24 (1.19-8.79)	0.021
Diagnosis of STEMI	5.50 (1.91-15.85)	0.002
Warfarin use	4.47 (1.33-15.02)	0.015
Thrombolysis	4.02 (2.18-7.39)	<0.001

Variables in adjusted model: age, gender, smoker, diabetes, hypertension, hypercholesterolaemia, thrombolysis, previous myocardial infarction, previous stroke, peripheral vascular disease, valvular heart disease, previous PCI, previous CABG, cardiogenic shock, receipt of circulatory support, thrombus aspiration, receipt of ventilation, left main stem PCI, diagnosis of NSTEMI, diagnosis of STEMI, receipt of glycoprotein IIb/IIIa inhibitor use, aspirin use, clopidogrel use, prasugrel use, ticagrelor use, ticlopidine use and warfarin use.

Table 4: Exploration of how significant predictors of ischaemic and haemorrhagic stroke complications change over time*

Variable	2007	2008	2009	2010	2011	2012	p-value
Ischaemic stroke							
Age (95% CI)	64.20 (64.11-64.29)	64.40 (64.31-64.49)	64.90 (64.81-64.99)	64.90 (64.81-64.99)	65.20 (65.11-65.29)	65.10 (65.02-65.18)	<0.001
Male gender (%, 95% CI)	45,250/61,191 (73.95, 73.60-74.30%)	49,014/66,194 (74.05, 73.72-74.38%)	52,129/70,531 (73.91, 73.59-74.23%)	53,975/72,940 (74.00, 73.68-74.32%)	55,713/75,356 (73.93, 73.62-74.24%)	58,317/78,953 (73.86, 73.55-74.17%)	0.978
Previous stroke (%, 95% CI)	1,781/58,175 (3.06, 2.92-3.29%)	2,177/65,134 (3.34, 3.20-3.48%)	2,840/69,595 (4.08, 3.93-4.23%)	2,917/71,897 (4.06, 3.92-4.20%)	3,144/74,133 (4.24, 4.09-4.39%)	3,187/77,341 (4.12, 3.98-4.26%)	<0.001
Previous valvular heart disease (%, 95% CI)	512/61,360 (0.83, 0.76-0.90%)	583/66,254 (0.88, 0.81-0.95%)	675/70,602 (0.96, 0.89-1.03%)	831/73,083 (1.14, 1.06-1.22%)	951/75,688 (1.26, 1.18-1.34%)	1,177/79,055 (1.49, 1.41-1.57%)	<0.001
Receipt of circulatory support (%, 95% CI)	1,015/52,087 (1.95, 1.83-2.07%)	1,131/60,784 (1.86, 1.75-1.97%)	1,325/65,305 (2.03, 1.92-2.14%)	1,510/68,388 (2.21, 2.10-2.32%)	1,671/72,581 (2.30, 2.19-2.41%)	1,741/76,530 (2.27, 2.16-2.38%)	<0.001
Thrombus aspiration (%, 95% CI)	1,032/52,989 (1.95, 1.83-2.07%)	3,050/61,187 (4.98, 4.81-5.15%)	6,864/66,536 (10.32, 10.09-10.55%)	10,084/68,896 (14.64, 14.38-14.90%)	11,937/72,237 (16.52, 16.25-16.79%)	13,048/75,945 (17.18, 16.91-17.45%)	<0.001
Diagnosis Stable angina (%,95% CI) NSTEMI (%,95% CI) STEMI (%, 95% CI)	 26,863 (46.77, 46.36-47.18%) 23,302 (40.57, 40.17-40.97%) 7,275 (12.67, 12.40-12.94%)	 30,385 (46.64, 46.26-47.02%) 24,620 (37.79, 37.42-38.16%) 10,137 (15.56, 15.28-15.84%)	 30,028 (42.79, 42.42-43.16%) 26,445 (37.68, 37.32-38.04%) 13,704 (19.53, 19.24-19.82%)	 28,650 (39.44, 39.08-39.80%) 26,997 (37.17, 36.82-37.52%) 16,987 (23.39, 23.08-23.70%)	 27,974 (37.15, 36.80-37.50%) 27,654 (36.73, 36.39-37.07%) 19,666 (26.12, 25.81-26.43%)	 28,754 (36.49, 36.15-36.83%) 28,747 (36.48, 36.14-36.82%) 21,303 (27.03, 26.72-27.34%)	<0.001

Haemorrhagic stroke							
Age (95% CI)	64.20 (64.11-64.29)	64.40 (64.31-64.49)	64.90 (64.81-64.99)	64.90 (64.81-64.99)	65.20 (65.11-65.29)	65.10 (65.02-65.18)	<0.001
Previous valvular heart disease (%, 95% CI)	512/61,360 (0.83, 0.76-0.90%)	583/66,254 (0.88, 0.81-0.95%)	675/70,602 (0.96, 0.89-1.03%)	831/73,083 (1.14, 1.06-1.22%)	951/75,688 (1.26, 1.18-1.34%)	1,177/79,055 (1.49, 1.41-1.57%)	<0.001
Diagnosis							<0.001
Stable angina (%,95% CI)	26,863 (46.77, 46.36-47.18%)	30,385 (46.64, 46.26-47.02%)	30,028 (42.79, 42.42-43.16%)	28,650 (39.44, 39.08-39.80%)	27,974 (37.15, 36.80-37.50%)	28,754 (36.49, 36.15-36.83%)	
NSTEMI (%,95% CI)	23,302 (40.57, 40.17-40.97%)	24,620 (37.79, 37.42-38.16%)	26,445 (37.68, 37.32-38.04%)	26,997 (37.17, 36.82-37.52%)	27,654 (36.73, 36.39-37.07%)	28,747 (36.48, 36.14-36.82%)	
STEMI (%, 95% CI)	7,275 (12.67, 12.40-12.94%)	10,137 (15.56, 15.28-15.84%)	13,704 (19.53, 19.24-19.82%)	16,987 (23.39, 23.08-23.70%)	19,666 (26.12, 25.81-26.43%)	21,303 (27.03, 26.72-27.34%)	
Warfarin	445/51,290 (0.87, 0.79-0.95%)	542/60,672 (0.89, 0.82-0.96%)	662/66,027 (1.00, 0.92-1.08%)	633/69,146 (0.92, 0.85-0.99%)	657/72,468 (0.91, 0.84-0.98%)	851/75,880 (1.12, 1.05-1.19%)	<0.001
Thrombolysis	4,701/50,769 (9.26, 9.01-9.51%)	4,828/59,539 (8.11, 7.89-8.33%)	4,108/64,633 (6.36, 6.17-6.55%)	2,911/67,827 (4.29, 4.14-4.44%)	1,329/69,981 (1.90, 1.80-2.00%)	848/73,173 (1.16, 1.08-1.24%)	<0.001

*Oneway analysis of variance for continuous data. Chi^2 test used to compare categorical data.

Table 5: Risk of adverse outcomes with unadjusted, adjusted and imputed results for participants with ischaemic stroke/TIA and haemorrhagic stroke

Variable	No stroke	Ischaemic stroke/TIA	P-value	Haemorrhagic stroke	P-value
MACE					
Unadjusted (n=426,190)	1.00 (ref)	8.34 (6.48-10.73)	<0.001	37.76 (25.83-55.21)	<0.001
Pseudo R^2		0.0018		0.0025	<0.001
Adjusted model (n=227,100)	1.00 (ref)	3.13 (1.84-5.30)	<0.001	13.19 (6.15-28.30)	<0.001
Pseudo R^2		0.0671		0.0675	
Adjusted model with imputation (n=360,500)	1.00 (ref)	3.03 (1.95-4.70)	<0.001	9.49 (4.93-18.27)	
30 day mortality					
Unadjusted (n=426,190)	1.00 (ref)	9.27 (7.18-11.99)	<0.001	44.16 (30.20-64.58)	<0.001
Pseudo R^2		0.0021		0.0030	
Adjusted model (n=229,362)	1.00 (ref)	4.94 (3.07-7.93)	<0.001	13.83 (6.35-30.12)	<0.001
Pseudo R^2		0.5012		0.5009	
Adjusted model with imputations (n=364,512)	1.00 (ref)	3.10 (2.02-4.75)	<0.001	10.14 (5.34-19.25)	<0.001

Adjusted model: adjusted for age, sex, smoking status, diabetes, hypertension, hypercholesterolaemia, previous MI, previous CVA, peripheral vascular disease, renal disease, previous valve disease, previous PCI, previous CABG, radial access site, cardiogenic shock, receipt of circulatory support, thrombus aspiration, ventilation, left main stem revascularization, diagnosis, glycoprotein IIb/IIIa, aspirin, clopidogrel, prasugrel, ticagrelor, ticlopidine, warfarin and thrombolysis

Table 6: Propensity score matched simple logistic regression analyses with multiple imputation, odds of adverse outcomes*†

Event	Outcome	Odds ratio (95% CI)	p-value
Ischaemic stroke/TIA	Mortality at 30 days	2.66 (1.97-3.60)	<0.001
	MACE	2.54 (1.88-3.42)	<0.001
Haemorrhagic stroke	Mortality at 30 days	4.08 (2.61-6.38)	<0.001
	MACE	3.83 (2.45-5.98)	<0.001
Ischaemic stroke only	Mortality at 30 days	2.79 (1.96-3.97)	<0.001
	MACE	2.62 (1.84-3.72)	<0.001
TIA only	Mortality at 30 days	1.85 (1.02-3.35)	0.042
	MACE	1.82 (1.03-3.24)	0.041

* one to ten matching when possible (propensity score difference below 10^{-5})

† Propensity score for 'control'/'treatment' groups calculated using age, sex, smoker, cardiogenic shock, diagnosis, previous MI, previous CABG, previous PCI, diabetes, year, left main stem, glycoprotein IIb/IIIa inhibitor use, circulatory support, hypercholesterolaemia, hypertension, previous stroke, valvular heart disease, renal disease, receipt of ventilation, aspirin use, clopidogrel use, warfarin use, prasugrel use, ticagrelor use, ticlopidine use, thrombus aspiration, femoral access and recent thrombolysis

Supplementary Table 1: Patient characteristics for included participants and excluded participants

Variable	Included in analysis (n=426,297)	Excluded from analysis (n=12,103)	P-value
Age	64.8 (±11.7)	64.8 (±11.7)	0.545
Female	110,835/425,410 (74.0%)	8,771/12,044 (72.8%)	0.006
Smoking	242,279/374,490 (64.7%)	6,404/10,272 (62.3%)	<0.001
Diabetes	76,909/407,703 (18.9%)	2,151/11,164 (19.3%)	0.283
Hypertension	219,977/416,523 (52.8%)	4,757/9,127 (52.1%)	0.190
Hyperlipidaemia	233,136/416,523 (56.0%)	4,555/9,127 (49.9%)	<0.001
Previous MI	107,055/380,039 (28.2%)	2,985/11,044 (27.0%)	0.009
Previous CVA	16,056/416,523 (3.9%)	294/9,127 (3.2%)	0.002
Peripheral vascular disease	19,781/416,523 (4.8%)	476/9,127 (5.2%)	0.038
Renal disease	10,805/403,697 (2.7%)	335/10,573 (3.2%)	0.002
Previous valve disease	4,733/426,293 (1.1%)	9/139 (6.5%)	<0.001
Previous PCI	90,659/408,933 (22.2%)	2,665/11,233 (23.7%)	<0.001
Previous CABG	34,398/407,887 (8.4%)	1,106/11,130 (9.9%)	<0.001
Access site Femoral Radial	 226,188 (56.0%) 177,458 (44.0%)	 5,369 (47.3%) 5,995 (52.8%)	<0.001
Cardiogenic shock	8,095/398,035 (2.0%)	269/10,920 (2.5%)	0.002
Use of circulatory support	8,405/395,902 (2.1%)	312/9,812 (3.2%)	<0.001
Thrombus aspiration	46,044/398,029 (11.6%)	1,500/10,822 (13.9%)	<0.001
Ventilatory support	4,924/355,928 (1.4%)	158/9,816 (1.6%)	0.059
Left Main Stem	13,176/412,350 (3.2%)	396/9,818 (4.0%)	<0.001
Diagnosis Stable angina NSTEMI STEMI	 172,745 (41.2%) 157,871 (37.6%) 89,118 (21.2%)	 4,647 (38.9%) 4,381 (36.7%) 2,921 (24.5%)	<0.001
Glycoprotein IIb/IIIa	88,269/373,396 (23.6%)	1,929/8,572 (22.5%)	0.014
Aspirin	330,610/395,728 (83.5%)	8,302/9,252 (89.7%)	<0.001
Clopidogrel	305,475/395,728 (77.2%)	7,077/9,252 (76.5%)	0.112
Prasugrel	13,498/395,728 (3.4%)	579/9,252 (6.3%)	<0.001
Ticagrelor	2,784/395,728 (0.7%)	247/9,252 (2.7%)	<0.001
Ticlopidine	1,364/395,728 (0.3%)	54/9,252 (0.6%)	<0.001
Warfarin	3,792/395,728 (1.0%)	101/9,252 (1.1%)	0.194
Thrombolysis	18,739/386,154 (4.9%)	476/10,689 (4.5%)	0.058
30-day mortality	8,724/426,297 (2.1%)	244/12,103 (2.0%)	0.816

Supplementary Table 2: Included and missing data

Variable	Included in analysis	Missing
Stroke type	426,436 (97.3%)	11,964 (2.7%)
Age	438,136 (99.9%)	264 (0.1%)
Gender	437,454 (99.8%)	946 (0.2%)
Smoking status	384,762 (87.8%)	53,638 (12.2%)
Diabetes	418,867 (95.5%)	19,533 (4.5%)
Hypertension	425,650 (97.1%)	12,750 (2.9%)
Hypercholesterolaemia	425,650 (97.1%)	12,750 (2.9%)
Previous myocardial infarction	391,083 (89.2%)	47,317 (10.8%)
Previous stroke	425,650 (97.1%)	12,750 (2.9%)
Peripheral vascular disease	425,650 (97.1%)	12,750 (2.9%)
Renal disease	414,270 (94.5%)	24,130 (5.5%)
Valvular heart disease	426,432 (97.3%)	11,968 (2.7%)
Previous PCI	420,166 (95.8%)	18,234 (4.2%)
Previous CABG	419,017 (95.6%)	19,383 (4.4%)
Access site	415,010 (94.7%)	23,390 (5.3%)
Cardiogenic shock	408,955 (93.3%)	29,445 (6.7%)
Circulatory support	405,714 (92.5%)	32,686 (7.5%)
Thrombus aspiration	408,851 (93.3%)	29,549 (6.7%)
Ventilatory support	365,744 (83.4%)	72,656 (16.6%)
Left main stem disease	422,168 (96.3%)	16,232 (3.7%)
Diagnosis	431,683 (98.5%)	6,717 (1.5%)
Glycoprotein IIb/IIIa inhibitor use	381,968 (87.1%)	56,432 (12.9%)
Aspirin use	404,980 (92.4%)	33,420 (7.6%)
Clopidogrel use	404,980 (92.4%)	33,420 (7.6%)
Prasugrel use	404,980 (92.4%)	33,420 (7.6%)
Ticagrelor use	404,980 (92.4%)	33,420 (7.6%)
Ticlopidine use	404,980 (92.4%)	33,420 (7.6%)
Warfarin use	404,980 (92.4%)	33,420 (7.6%)
Thrombolysis use	396,843 (90.5%)	41,557 (9.5%)
MACE	426,575 (96.3%)	11,825 (2.7%)
30 day mortality	438,400 (100%)	0 (0%)

PCI=percutaneous coronary intervention, CABG=coronary artery bypass graft

Supplementary Table 3: Missing data by year of procedure

Variable	2007 (n=63,437)	2008 (n=68,285)	2009 (n=71,716)	2010 (n=75,044)	2011 (n=78,376)	2012 (n=81,542)
Age	47 (0.07%)	31 (0.05%)	33 (0.05%)	74 (0.10%)	58 (0.07%)	21 (0.03%)
Gender	178 (0.38%)	70 (0.10%)	77 (0.11%)	158 (0.21%)	361 (0.46%)	102 (0.13%)
Smoking status	11,801 (18.60%)	9,703 (14.21%)	7,616 (10.62%)	8,366 (11.15%)	7,997 (10.20%)	8,155 (10.00%)
Diabetes	4,685 (7.39%)	2,817 (4.13%)	2,058 (2.87%)	2,688 (3.58%)	2,899 (3.70%)	4,386 (5.38%)
Hypertension	4,329 (6.82%)	1,917 (2.81%)	1,227 (1.71%)	1,339 (1.78%)	1,976 (2.52%)	1,962 (2.41%)
Hypercholesterolaemia	4,329 (6.82%)	1,917 (2.81%)	1,227 (1.71%)	1,339 (1.78%)	1,976 (2.52%)	1,962 (2.41%)
Previous myocardial infarction	10,623 (16.75%)	9,690 (14.19%)	8,067 (11.25%)	6,710 (8.94%)	6,044 (7.71%)	6,183 (7.58%)
Previous stroke	4,329 (6.82%)	1,917 (2.81%)	1,227 (1.71%)	1,339 (1.78%)	1,976 (2.52%)	1,962 (2.41%)
Peripheral vascular disease	4,329 (6.82%)	1,917 (2.81%)	1,227 (1.71%)	1,339 (1.78%)	1,976 (2.52%)	1,962 (2.41%)
Renal disease	6,580 (10.37%)	3,659 (5.36%)	2,548 (3.55%)	3,766 (5.02%)	3,871 (4.94%)	3,706 (4.54%)
Valvular heart disease	2,016 (3.18%)	1,964 (2.88%)	1,065 (1.49%)	1,865 (2.49%)	2,613 (3.33%)	2,445 (3.00%)
Previous PCI	6,219 (9.80%)	3,606 (5.28%)	2,462 (3.43%)	1,749 (2.33%)	2,012 (2.57%)	2,186 (2.68%)
Previous CABG	5,248 (8.27%)	3,607 (5.28%)	3,363 (4.69%)	2,857 (3.81%)	2,436 (3.11%)	1,872 (2.30%)
Access site	5,236 (8.25%)	4,492 (6.58%)	2,989 (4.17%)	3,425 (4.56%)	3,508 (4.48%)	3,740 (4.59%)
Cardiogenic shock	8,065 (12.71%)	4,610 (6.75%)	4,277 (5.96%)	4,152 (5.53%)	4,421 (5.64%)	3,920 (4.81%)
Circulatory support	9,867 (15.55%)	5,632 (8.25%)	5,413 (7.55%)	4,963 (6.61%)	3,369 (4.30%)	3,442 (4.22%)
Thrombus aspiration	8,448 (13.32%)	5,107 (7.48%)	4,111 (5.73%)	4,311 (5.74%)	3,674 (4.69%)	3,898 (4.78%)
Ventilatory support	16,319 (25.72%)	15,368 (21.04%)	11,692 (16.30%)	11,036 (14.71%)	9,898 (12.63%)	9,343 (11.46%)
Left main stem disease	4,964 (7.83%)	2,395 (3.51%)	1,923 (2.68%)	2,673/75,044 (3.56%)	2,079 (2.65%)	2,198 (2.70%)
Diagnosis	3,939 (6.21%)	1,130 (1.65%)	447 (0.62%)	462 (0.62%)	425 (0.54%)	314 (0.39%)
Glycoprotein IIb/IIIa inhibitor use	11,147 (17.57%)	9,445 (13.83%)	9,094 (12.12%)	9,094 (12.12%)	9,240 (12.12%)	9,240 (11.79%)

Aspirin use	10,807 (17.04%)	6,086 (8.91%)	4,698 (6.55%)	4,169 (5.56%)	3,935 (5.02%)	3,725 (4.57%)
Clopidogrel use	10,807 (17.04%)	6,086 (8.91%)	4,698 (6.55%)	4,169 (5.56%)	3,935 (5.02%)	3,725 (4.57%)
Prasugrel use	10,807 (17.04%)	6,086 (8.91%)	4,698 (6.55%)	4,169 (5.56%)	3,935 (5.02%)	3,725 (4.57%)
Ticagrelor use	10,807 (17.04%)	6,086 (8.91%)	4,698 (6.55%)	4,169 (5.56%)	3,935 (5.02%)	3,725 (4.57%)
Ticlopidine use	10,807 (17.04%)	6,086 (8.91%)	4,698 (6.55%)	4,169 (5.56%)	3,935 (5.02%)	3,725 (4.57%)
Warfarin use	10,807 (17.04%)	6,086 (8.91%)	4,698 (6.55%)	4,169 (5.56%)	3,935 (5.02%)	3,725 (4.57%)
Thrombolysis use	10,690 (16.85%)	6,837 (10.01%)	6,099 (8.50%)	5,360 (7.14%)	5,945 (7.59%)	6,626 (8.13%)
MACE	2,008 (3.17%)	1,951 (2.86%)	1,037 (1.45%)	1.832 (2.44%)	2,585 (3.30%)	2,412 (2.96%)
30 day mortality	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

PCI=percutaneous coronary intervention, CABG=coronary artery bypass graft

Supplementary Table 4: Stroke and TIA events by year of PCI

Stroke/TIA type	2007	2008	2009	2010	2011	2012	Total
Ischaemic stroke/TIA	41/61,387 (0.067%)	52/66,267 (0.078%)	77/70,608 (0.109%)	85/73,132 (0.116%)	91/75,734 (0.120%)	90/79,062 (0.114%)	436/426,190 (0.102%)
Events/1000 patients (95% CI)	0.67 (0.47-0.87)	0.78 (0.58-0.98)	1.09 (0.89-1.29)	1.16 (0.96-1.36)	1.20 (1.00-1.40)	1.14 (0.94-1.34)	1.02 (0.92-1.12)
Haemorrhagic stroke	18/61,364 (0.029%)	22/66,237 (0.033%)	25/70,556 (0.035%)	22/73,069 (0.030%)	8/75,651 (0.011%)	12/78,984 (0.015%)	107/425,861 (0.025%)
Events/1000 patients (95% CI)	0.29 (0.19-0.39)	0.33 (0.23-0.43)	0.35 (0.25-0.45)	0.30 (0.20-0.40)	0.11 (0.01-0.21)	0.15 (0.05-0.25)	0.25 (0.20-0.30)
Ischaemic stroke	20/61,366 (0.033%)	33/66,248 (0.050%)	38/70,569 (0.054%)	62/73,109 (0.085%)	49/75,692 (0.065%)	59/79,031 (0.075%)	261/426,015 (0.061%)
Events/1000 patients (95% CI)	0.33 (0.23-0.43)	0.50 (0.30-0.70)	0.54 (0.34-0.74)	0.85 (0.65-1.05)	0.65 (0.45-0.85)	0.75 (0.55-0.95)	0.61 (0.51-0.71)
TIA	21/61,367 (0.034%)	19/66,234 (0.029%)	39/70,570 (0.055%)	23/73,070 (0.031%)	42/75,685 (0.055%)	31/79,003 (0.039%)	175/425,929 (0.041%)
Events/1000 patients (95% CI)	0.34 (0.24-0.44)	0.29 (0.19-0.39)	0.55 (0.35-0.75)	0.31 (0.21-0.41)	0.55 (0.35-0.75)	0.39 (0.29-0.49)	0.41 (0.31-0.51)

Supplementary Table 5: Crude adverse event rates by stroke/TIA group

Group	MACE	Mortality at 30 days
Ischaemic stroke/TIA		
Yes	73/436 (17%)	70/436 (16%)
No	10,026/425,754 (2%)	8,603/425,754 (2%)
Haemorrhagic stroke		
Yes	51/107 (48%)	51/107 (48%)
No	10,026/425,754 (2%)	8,603/425,754 (2%)
Ischaemic stroke		
Yes	57/261 (22%)	55/261 (21%)
No	10,026/425,754 (2%)	8,603/425,754 (2%)
TIA		
Yes	16/175 (9%)	15/175 (9%)
No	10,026/425,754 (2%)	8,603/425,754 (2%)

Supplementary Table 6: Risk of adverse outcomes with unadjusted, adjusted and imputed results for participants in ischaemic stroke and TIA

Variable	No stroke	Ischaemic stroke	P-value	TIA	P-value
MACE					
Unadjusted (n=426,015)	1.00 (ref)	11.59 (8.63-15.55)	<0.001	4.17 (2.49-6.98)	<0.001
Pseudo R^2		0.0017		0.0002	
Adjusted model (n=226,999)	1.00 (ref)	3.16 (1.65-6.07)	<0.001	3.07 (1.26-7.48)	0.014
Pseudo R^2		0.0667		0.0665	
Adjusted model with imputation (n=360,350)	1.00 (ref)	3.11 (1.79-5.39)	<0.001	2.91 (1.40-6.02)	0.004
30 day mortality					
Unadjusted (n=426,015)	1.00 (ref)	12.95 (9.61-17.45)	<0.001	4.55 (2.68-7.72)	<0.001
Pseudo R^2		0.0020		0.0003	
Adjusted model (n=229,255)	1.00 (ref)	4.79 (2.68-8.57)	<0.001	5.24 (2.32-11.81)	<0.001
Pseudo R^2		0.5008		0.4997	
Adjusted model with imputations (n=364,356)	1.00 (ref)	3.32 (1.98-5.56)	<0.001	2.69 (1.25-5.77)	0.011

Adjusted model: adjusted for age, sex, smoking status, diabetes, hypertension, hypercholesterolaemia, previous MI, previous CVA, peripheral vascular disease, renal disease, previous valve disease, previous PCI, previous CABG, radial access site, cardiogenic shock, receipt of circulatory support, thrombus aspiration, ventilation, left main stem revascularization, diagnosis, glycoprotein IIb/IIIa, aspirin, clopidogrel, prasugrel, ticagrelor, ticlopidine, warfarin and thrombolysis

Supplementary Table 7: Propensity scores for comparison groups*†

Event		Mean	Standard Deviation
Ischaemic stroke/TIA	No	0.00107	0.00168
	Yes	0.00311	0.00418
Haemorrhagic stroke	No	0.00027	0.00126
	Yes	0.00557	0.01243
Ischaemic stroke only	No	0.00064	0.00139
	Yes	0.00307	0.00535
TIA only	No	0.00043	0.00048
	Yes	0.00090	0.00083

* Propensity score for 'control'/'treatment' groups calculated using age, sex, smoker, cardiogenic shock, diagnosis, previous MI, previous CABG, previous PCI, diabetes, year, left main stem, glycoprotein IIb/IIIa inhibitor use, circulatory support, hypercholesterolaemia, hypertension, previous stroke, valvular heart disease, renal disease, receipt of ventilation, aspirin use, clopidogrel use, warfarin use, prasugrel use, ticagrelor use, ticlopidine use, thrombus aspiration, femoral access and recent thrombolysis

† Across the 10 datasets used in the multiple imputation processes