Determinants and outcomes of stroke following percutaneous coronary intervention by indication

Cover title: Stroke following Elective versus ACS PCI

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Abstract

Background and Purpose: Stroke following percutaneous coronary intervention (PCI) is a serious complication, but its determinants and outcomes following PCI in different clinical settings are poorly documented.

Methods: The British Cardiovascular Intervention Society (BCIS) database was used to study 560,439 patients who underwent PCI in England and Wales between 2006 and 2013. We examined procedural type specific determinants of ischemic and hemorrhagic stroke and the likelihood of subsequent 30-day mortality and in-hospital major adverse cardiovascular events (MACE; a composite of in-hospital mortality, myocardial infarction or re-infarction and repeat revascularization).

Results: A total of 705 stroke cases were recorded (80% ischemic). Stroke following an elective PCI or PCI for ACS indications was associated with a higher risk of adverse outcomes compared to those without stroke; 30-day mortality and MACE outcomes in fully adjusted model were ORs 37.90(21.43-67.05) and 21.05 (13.25-33.44) for elective and 5.00(3.96-6.31) and 6.25(5.03-7.77) for ACS, respectively. Comparison of odds of these outcomes between these two settings showed no differences; corresponding ORs were 1.24(0.64-2.43) and 0.63(0.35-1.15), respectively.

Conclusions: Hemorrhagic and ischemic stroke complications are uncommon but serious complications that can occur following PCI and are independently associated with worse mortality and MACE outcomes in both the elective and ACS setting irrespective of stroke type. Our study provides a better understanding of the risk factors and prognosis of stroke following PCI by procedure type allowing physicians to provide more informed advice around stroke risk following PCI and counsel patients and their families around outcomes if such neurological complications occur.

Introduction

Stroke is a serious complication following percutaneous coronary intervention (PCI). We and others have previously shown that it is associated with high in-hospital mortality [1-4] and causes life changing disabilities in those who survive [5-7]. Previous studies were conducted in both single centre [8-9] and multicentre settings [1,2] and reported the incidence, major determinants and outcomes of stroke following PCI.

PCI is performed either electively or in the setting of an acute coronary syndrome (ACS) as a non-elective (urgent/emergency) procedure. The clinical and procedural characteristics in these two settings are different [10,11], and it is conceivable that risk factors for stroke during these two clinical scenarios are likely to differ with different impacts on 30-day mortality and MACE (in-hospital major adverse cardiovascular events) associated with stroke. Indeed, Werner and colleagues have recently reported differences in determinants of stroke in different clinical settings but were unable to examine this issue specifically for ischemic and hemorrhagic stroke separately [2]. Better understanding of such determinants is important as these stroke subtypes have different pathophysiologies, different risk profiles and different survival trajectories [12]. These cannot be tested in randomised trial setting and such real world events needed to be observed and reported through registry data.

In this study, we examined the determinants and outcomes of ischemic and hemorrhagic stroke associated with PCI for ACS compared with those who underwent elective PCI using the British Cardiovascular Intervention Society registry in England and Wales including over half a million participants. The key objectives of the current study are therefore (1) to examine (a) the determinants and (b) factors associated with mortality and MACE following ischemic and hemorrhagic stroke following PCI in the ACS and elective

settings separately; and (2) to compare the outcomes of the strokes following PCI between two clinical settings.

Methods

Data for the current study were taken from the British Cardiovascular Intervention Society (BCIS) dataset, which records all PCI procedures conducted in the UK. The data contains over 100 variables on clinical, procedural and outcome information with approximately ~80,000 new records added each year. In-hospital outcomes are recorded on the database and mortality outcomes tracked through the Medical Research Information Service (MRIS) using the patients' National Health Service number.

The main exposure variable for the analysis was whether the PCI procedure was carried out as an elective or for ACS. The main outcomes were in-hospital MACE and 30-day mortality associated with stroke following PCI. Major adverse cardiac events (MACE) were defined as a composite of in hospital mortality, myocardial infarction or repeat intervention. We defined stroke-related mortality as mortality among patients who developed stroke complications after PCI. Other variables included as potential confounders are described in **Supplementary Data 1**.

Statistical analysis

Statistical analyses were performed using Stata Version 13.0 (College Station, Texas, USA). Descriptive statistics were presented by indication (elective cases or PCI for acute coronary syndrome) and stroke subtype (ischemic and hemorrhagic stroke). Multiple imputations by chained equations were used to account for missing variables with 10 imputed datasets. All the non-outcome variables were then put into multiple logistic regression models to identify independent predictors of ischemic and hemorrhagic stroke subtypes separately according to indication of PCI. To calculate the impact of ischemic stroke and

hemorrhagic stroke on in-hospital MACE and 30-day mortality, we used multiple logistic regressions controlled for all available covariates and executed separately for elective and ACS.

We then assessed the odds of these adverse outcomes in PCI for ACS using elective PCI procedure as the reference category in those who had stroke as a complication of PCI. We used a step-wise modeling approach to better understand the associations and the following models were constructed. The models are described in **Supplementary Data 1**.

To account for baseline differences across stroke groups, multiple imputations with propensity score matching (*mi estimate: teffects psmatch* on Stata) was used to estimate the average treatment effect (ATE). The method was used to analyze two separate logistic treatment models (ischemic stroke vs. no stroke and any stroke vs. no stroke), calculating propensity scores for group membership. Additional descriptions of the analysis methods are described in **Supplementary Data 1**.

Results

A total of 588,636 patients underwent either elective PCI or PCI for ACS in England and Wales between 2006 and 2013. After exclusion of 28,197 patients with missing information on stroke subtype, indication for PCI, age, and sex, a total of 560,439 patients were included in the analysis. More than 50% of variables (14/25) had missing data less than 5%, and 80% (20/25) had <10% missing values **(Supplementary Table 1)**. A total of 705 patients (0.13%) experienced an in-patient stroke complication following PCI of whom 566 patients (0.10%) sustained an ischemic stroke and 139 patients (0.02%) sustained a hemorrhagic stroke.

Table 1 shows the differences in the sample characteristics between patients who had ischemic and hemorrhagic stroke and those who did not stratified by PCI setting. Older age,

female sex and requirement to use glycoprotein IIb/IIIa inhibitors were significantly associated with ischemic stroke as a complication after elective PCI. Patients with a confirmed stroke post elective PCI had a significantly higher incidence of in-hospital MACE and 30-day mortality. In the setting of PCI for ACS, the demographic profile associated with an ischemic stroke was similar, but with a wider age difference; mean age difference was 5.4 years compared to 2.2 years observed in the elective setting. Female sex, history of previous stroke, cardiogenic shock and requirement for circulatory support, glycoprotein IIb/IIIa inhibitor use and left main stem disease were significantly associated with the complication of hemorrhagic stroke post elective PCI. Those with hemorrhagic stroke post elective PCI had a considerably higher rate of in-hospital MACE and 30-day mortality than those without stroke.

The risk factor profile for hemorrhagic stroke in the ACS setting was similar to the risk factor profile for ischemic stroke except for higher prevalence of valvular heart disease and left main stem disease, and greater use of thrombectomy in those with ischemic strokes, while patients with hemorrhagic strokes were more likely to have a diagnosis of hyperlipidemia and were more often treated with thrombolysis.

Tables 2 & 3 show the significant independent predictors of ischemic stroke and hemorrhagic stroke outcomes stratified by the clinical setting of the PCI procedure. Only female sex and the requirement for glycoprotein IIb/IIIa inhibitors significantly predicted ischemic stroke post elective PCI. Older age, female sex, previous history of stroke and CABG, prior use of warfarin, presentation with STEMI, cardiogenic shock, the requirement of circulatory and ventilatory support, and thrombectomy were identified as significant predictors of ischemic stroke following PCI for ACS.

Independent predictors of hemorrhagic stroke in elective PCI included female sex, history of previous stroke, previous PCI and glycoprotein IIb/IIIa inhibitor use, whilst older

age, previous PCI, STEMI, cardiogenic shock, requirement for circulatory and ventilator support, and thrombolysis were independent predictors of hemorrhagic stroke in the PCI for ACS setting.

Table 4 & **Supplementary Table 2** shows the association between the occurrence of a stroke complication and in-hospital MACE and 30-day mortality following multivariate analysis, both for the individual stroke subtypes and the combined stroke cohort. All analyses consistently show that having a stroke complication (either ischemic or hemorrhagic stroke) was significantly associated with poor outcomes assessed regardless of the clinical setting in which it occurred. Finally, ischemic stroke complications following PCI for ACS were associated with a significantly increased risk of in-hospital MACE but not 30-day mortality after controlling for various potential confounders compared to stroke complications after elective PCI.

Supplementary Table 3 shows the results with logistic regression following propensity score matching. This analysis suggests a significant increase in in-hospital MACE for total and ischemic stroke in both settings. There were insufficient events to perform the propensity score matching analysis for hemorrhagic stroke. After propensity score matching, there were significant increases in in-hospital MACE for ischemic and any stroke following both PCI procedures. For 30-day mortality, similar significant increases were observed except for any stroke in elective patients.

Discussion

Our analysis of the UK national PCI database of over half a million patients undergoing PCI suggests that stroke is very uncommon after PCI. However, once stroke occurs as a complication of PCI, 30-day mortality and MACE are high, both in cerebral

infarcts and hemorrhages. Surprisingly the odds of both these complications are higher following an elective procedure than for ACS, as patients with ACS are likely to be sicker and have a worse risk profile compared to elective patients. Patients undergoing elective PCI were usually treated with clopidogrel at the time of the procedure, while the majority of patients undergoing emergency PCI were more likely to be on newer oral antiplatelet therapies such as ticagralor and prasugrel and also be treated with glycoprotein IIb/IIIa inhibitors that have more potent anti-platelet inhibition properties. This could potentially have had a protective effect in relation to ischemic stroke but also increase the risk of death after intracerebral hemorrhage in the ACS group.

Our work provides insight to the outcomes associated with this rare but devastating complication of PCI to the stroke physician, who may not frequently encounter such patients frequently treated with potent anti-platelet and anti-coagulant therapies, which are necessitated during the PCI procedure. To our knowledge, this is the first paper to examine the determinants and outcomes of stroke following PCI by the indication as well as by specific stroke subtype. The key strength of our work is its large sample size and our ability to control for various potential confounders in an unselected cohort of patients undergoing PCI.

Our data builds on the report of Werner and colleagues who examined stroke risk stratified by the clinical setting of the PCI procedure [2], by additionally demonstrating that risk factors for ischemic and hemorrhagic stroke also vary by the clinical setting of the PCI procedure. Cardiovascular risk factors appear to be major determinants of risk of developing ischemic stroke in ACS setting, whilst the stroke risk for elective PCI is associated with glycoprotein IIb/IIIa usage. This observation may relate to the fact that glycoprotein IIb/IIIa is used in higher thrombotic risk patients in the elective setting (such as diabetics or those patients undergoing complex procedures) who are at higher risk of sustaining ischemic events

such as strokes [13,14]. It is possible that use of these agents is a marker for the various procedural complications or complexities that led an operator to use these agents. Supporting the findings from TOTAL [15], thrombectomy usage is also predictive of ischemic stroke after PCI for ACS. An important observation is the higher ischemic stroke risk observed for women for both indications for PCI (OR 2.62 and 1.78 respectively) compared to men.

It is interesting that age appears to be predictive of stroke complications only in ACS setting but not in elective PCI setting once potential confounders were adjusted for. Similar results are observed for risk of hemorrhagic stroke. Thus, age per se is not a risk factor for a stroke complication sustained following elective PCI. Werner and colleagues reported overall in-hospital mortality of 19.2% for patients who developed stroke (elective PCI, 10.0%; PCI for ACS, 23.2%) compared with 1.3% for those without stroke (elective PCI, 0.2%; PCI for ACS, 2.3%). These results are similar to the 30-day mortality reported in the current study of 18.9% (elective PCI, 6.7%; PCI for ACS, 21.2%) for those who developed stroke compared with 2.0% for those who did not (elective PCI, 0.3%; PCI for ACS, 3.2%).

We found the risk of adverse outcome (in-hospital MACE or 30-day mortality) to be significantly higher in patients where PCI was complicated by a stroke regardless of stroke subtype or the clinical setting that it occurred in. Whilst this finding is not unexpected, we found that the greatest observed risk for adverse outcomes is associated with in-hospital strokes complicating elective PCI. This appears to be more pronounced in hemorrhagic stroke albeit with large estimates perhaps contributed by the relatively small sample size compared to ischemic stroke. Finally, once stroke has occurred, the further risk of MACE and 30-day mortality is high, but not significantly different between the two settings. Considering that patients with PCI have significant cardiovascular morbidity in addition to the stroke, it is not surprising.

Our study has several strengths. The BCIS dataset includes >95% of all PCI procedures performed in the UK 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. Whilst stroke is a relatively rare complication of PCI, its impact on mortality and morbidity and residual long-term disability has profound consequences not only for patients and their carers but also purchasers and providers of healthcare. Our large sample size allows us to study risk factors for sustaining a stroke complication following two clinical settings in which PCI is performed, as well as enabling us to compare and contrast the risk of adverse outcomes by the clinical setting and also provide stroke subtype specific prognostic information in these settings. This will enable stroke physicians to better counsel patients and their families regarding outcomes.

There are also limitations in this study. Our dataset does not capture the timing and severity of stroke, stroke nature and ADL score. We are unable to ascertain the temporal relationship between the predictor and stroke event. For example, it is possible that patients who undergo ventilation are more likely to develop stroke but patients might also be ventilated as a consequence of developing stroke or patients who were admitted with a myocardial infarction may have sustained a stroke as a consequence of the coronary event rather than the procedure itself. However, the primary focus is to compare and contrast risk factors and outcomes of each stroke subtype for each type of PCI procedure. As highlighted in our previous work [4] the diagnosis of stroke is reported by individual operators with no external validation, or information how the diagnosis was reached or what imaging modalities were used to ascertain etiology hence there is the potential for under-reporting or misclassification of neurological events. In the UK however, it is standard practice that anyone who sustains a stroke is referred to a stroke team who would organize the relevant neuroimaging, confirm the diagnosis and offer guidance in management of the patient.

Furthermore, our reported incident stroke rates are similar in magnitude to those reported in the national NCDR [2] and the SCAAR [16] datasets derived from USA and Sweden respectively. Given the smaller proportion of hemorrhagic strokes within the total stroke population in this cohort, even with over half a million PCI procedures, we were not able to perform propensity score matched analyses. Finally, whilst the BCIS dataset captures PCI related complications, it does not capture information as to how these were managed or whether there were differences in the management of such complications between units.

In summary, we found that stroke after both the elective and ACS setting is associated with adverse outcomes, irrespective of stroke subtype. Our study provides a better understanding of the risk factors as well as outcomes for stroke following PCI by procedure type as well as specific stroke subtype. This will inform both clinicians and patients on stroke risk associated in a specific PCI setting, but also provides important outcome information from a national perspective, to enable stroke physicians to counsel patients and their families around outcomes if such neurological complications occur, since stroke complications occurring in this setting will represent a small proportion of stroke physicians case mix.

Disclosures

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Table 1: Sample characteristics between those who had stroke complication compared with those who did not by type of PCI procedure for ischemic and hemorrhagic stroke

Variable	No stroke elective	Ischemic stroke elective	P	No stroke non-elective	Ischemic stroke non-elective	P	No stroke elective	Hemorrhagic stroke elective	P	Hemorrhagic stroke non-elective	P
Age (years)	65.3±10.6	67.5±10.2	**0.048**	64.3±12.5	69.7±12.2	**<0.001**	65.3±10.6	67.8±9.9	0.19	69.3±10.9	**<0.001**
Female	57,572 (25%)	42 (46%)	**<0.001**	87,518 (27%)	201 (42%)	**<0.001**	57,572 (25%)	10 (45%)	**0.025**	45 (39%)	**0.003**
Diagnosis			0.96			**<0.001**			0.98		**<0.001**
Stable angina	218,300 (100%)	90 (100%)		834 (0.3%)	0 (0%)		218,300 (100%)	21 (100%)		0 (0%)	
NSTEMI	5 (0%)	0 (0%)		205,740 (67%)	181 (41%)		5 (0%)	0 (0%)		41 (46%)	
STEMI	0 (0%)	0 (0%)		102,189 (33%)	256 (59%)		0 (0%)	0 (0%)		48 (54%)	
Smoking status			0.055			0.11			0.24		0.28
Never smoked	78,871 (40%)	44 (52%)		94,614 (33%)	155 (38%)		79,871 (40%)	9 (47%)		38 (37%)	
Ex-smoker	93,682 (47%)	33 (39%)		101,110 (35%)	134 (33%)		93,682 (47%)	10 (53%)		39 (38%)	
Current smoker	25,491 (13%)	7 (8%)		91,583 (32%)	121 (30%)		25,491 (13%)	0 (0%)		25 (25%)	
Hypertension	129,431 (58%)	51 (59%)	0.91	155,469 (49%)	236 (50%)	0.44	129,431 (58%)	13 (57%)	0.92	60 (52%)	0.49
Hypercholesterolemia	139,321 (62%)	58 (67%)	0.42	160,693 (50%)	228 (49%)	0.51	139,321 (62%)	15 (68%)	0.58	47 (41%)	**0.038**
Diabetes	46,035 (21%)	21 (24%)	0.57	55,262 (18%)	83 (18%)	0.95	46,035 (21%)	3 (14%)	0.39	24 (21%)	0.31
Previous myocardial infarction	68,895 (34%)	29 (35%)	0.87	71,445 (24%)	108 (25%)	0.88	68,985 (34%)	4 (22%)	0.31	29 (26%)	0.66
Previous stroke	7,610 (3%)	5 (6%)	0.23	12,811 (4%)	40 (9%)	**<0.001**	7,610 (3%)	3 (14%)	**0.008**	9 (8%)	**0.039**
Peripheral vascular disease	10,834 (5%)	4 (5%)	0.91	14,571 (5%)	36 (8%)	**0.001**	10,834 (5%)	2 (9%)	0.36	10 (9%)	**0.035**
Renal disease	5,106 (2%)	1 (1%)	0.49	8,921 (3%)	20 (4%)	**0.043**	5,106 (2%)	1 (5%)	0.46	8 (7%)	**0.007**
Valvular heart disease	3,221 (1%)	2 (2%)	0.50	3,192 (1%)	9 (2%)	**0.045**	3,221 (1%)	0 (0%)	0.57	0 (0%)	0.28
Previous PCI	70,388 (32%)	32 (36%)	0.48	48,826 (16%)	69 (15%)	0.66	70,388 (32%)	9 (41%)	0.37	21 (18%)	0.35
Previous CABG	92,982 (40%)	36 (40%)	0.91	121,073 (37%)	149 (31%)	**0.012**	92,982 (40%)	12 (55%)	0.17	31 (27%)	**0.020**
Cardiogenic shock	0 (0%)	0 (0%)	0.76	10,755 (3%)	81 (17%)	**<0.001**	0 (0%)	0 (0%)	-	25 (22%)	**<0.001**
Receipt of ventilation	0 (0%)	0 (0%)	0.62	6,582 (2%)	50 (11%)	**<0.001**	0 (0%)	0 (0%)	-	13 (12%)	**<0.001**
Circulatory support	461 (0.2%)	0 (0%)	0.65	8,119 (3%)	79 (17%)	**<0.001**	461 (0.2%)	2 (9%)	**<0.001**	19 (17%)	**<0.001**
Antiplatelet therapy			0.55			0.13			0.89		0.18

Clopidogrel Prasugrel Ticagrelor	168,845 (98%) 1,717 (1%) 1,020 (0.6%)	73 (100%) 0 (0%) 0 (0%)		217,872 (89%) 16,108 (7%) 11,774 (5%)	311 (86%) 33 (9%) 19 (5%)		167,845 (98%) 1,717 (1%) 1,020 (0.6%)	15 (100%) 0 (0%) 0 (0%)		84 (94%) 4 (4%) 1 (1%)	
Warfarin use	2,822 (1%)	1 (1%)	0.92	2,405 (0.8%)	10 (2%)	**0.001**	2,822 (1%)	1 (5%)	0.14	3 (3%)	**0.022**
Glycoprotein IIb/IIIa inhibitor use	19,720 (9%)	30 (34%)	**<0.001**	101,572 (33%)	232 (50%)	**<0.001**	19,720 (9%)	8 (38%)	**<0.001**	49 (42%)	**0.038**
Thrombectomy use	0 (0%)	0 (0%)	-	46,927 (15%)	129 (28%)	**<0.001**	0 (0%)	0 (0%)	**-**	20 (18%)	0.55
Left main stem disease	7,970 (4%)	5 (6%)	0.33	10,501 (3%)	29 (6%)	**<0.001**	7,970 (4%)	3 (14%)	**0.009**	7 (6%)	0.10
Thrombolysis	0 (0%)	0 (0%)	-	22,100 (8%)	35 (8%)	0.84	0 (0%)	0 (0%)	-	30 (27%)	**<0.001**
In-hospital MACE	2,303 (1%)	23 (25%)	**<0.001**	9,363 (3%)	122 (26%)	**<0.001**	2,303 (1%)	4 (18%)	**<0.001**	43 (37%)	**<0.001**
Death at 30 days	757 (0.3%)	6 (7%)	**<0.001**	10,350 (3%)	99 (21%)	**<0.001**	757 (0.3%)	10 (45%)	**<0.001**	57 (51%)	**<0.001**

PCI=percutaneous coronary intervention, CABG=coronary artery bypass graft, MACE=major adverse cardiovascular event

Table 2: Significant predictors of ischemic stroke outcome by type of PCI

Variables	Elective PCI	P	Non-elective PCI	P
Age	1.01 (0.99-1.04)	0.19	**1.03 (1.02-1.04)**	**<0.001**
Female	**2.52 (1.65-3.86)**	**<0.001**	**1.78 (1.47-2.16)**	**<0.001**
Smoking status				
Non-smoker	1.00 (ref)	-	1.00 (ref)	-
Ex-smoker	0.74 (0.46-1.17)	0.20	0.95 (0.76-1.20)	0.70
Current smoker	0.60 (0.26-1.39)	0.23	1.07 (0.83-1.39)	0.61
Hypertension	0.86 (0.55-1.37)	0.53	0.95 (0.76-1.20)	0.64
Hypercholesterolemia	1.26 (0.78-2.03)	0.35	1.08 (0.88-1.32)	0.48
Diabetes	1.07 (0.65-1.76)	0.80	0.95 (0.74-1.22)	0.68
Previous myocardial infarction	1.06 (0.66-1.72)	0.81	1.08 (0.82-1.41)	0.59
Previous stroke	1.67 (0.66-4.18)	0.28	**1.70 (1.21-2.38)**	**0.002**
Peripheral vascular disease	0.81 (0.29-2.27)	0.70	1.31 (0.92-1.88)	0.14
Renal disease	0.50 (0.07-3.65)	0.50	1.25 (0.78-1.98)	0.35
Previous PCI	1.29 (0.80-2.06)	0.29	1.11 (0.82-1.50)	0.49
Previous CABG	0.99 (0.65-1.52)	0.97	**0.81 (0.66-0.99)**	**0.038**
Cardiogenic shock	-	-	**1.48 (1.03-2.12)**	**0.032**
Receipt of ventilation	-	-	**2.35 (1.64-3.37)**	**<0.001**
Circulatory support	-	-	**2.83 (2.02-3.97)**	**<0.001**
Antiplatelet therapy*		-		
Clopidogrel	-		1.00 (ref)	-
Prasugrel	-		1.05 (0.71-1.56)	0.81
Ticagrelor	-		1.02 (0.62-1.69)	0.93
Warfarin use	0.91 (0.13-6.62)	0.93	**2.22 (1.17-4.18)**	**0.014**
Glycoprotein IIb/IIIa inhibitor use	**5.39 (3.40-8.55)**	**<0.001**	**1.66 (1.36-2.03)**	**<0.001**
Left main stem disease	1.28 (0.52-3.19)	0.59	1.12 (0.75-1.67)	0.57
Thrombectomy	-	-	**1.40 (1.10-1.77)**	**0.006**
Recent thrombolysis	-	-	1.20 (0.84-1.72)	0.32
STEMI	**-**	**-**	**1.94 (1.55-2.43)**	**<0.001**
Year				
2006	1.00 (ref)	-	1.00 (ref)	-
2007	0.91 (0.39-2.12)	0.83	1.01(0.63-1.63)	0.97
2008	1.28 (0.59-2.79)	0.53	1.19 (0.76-1.87)	0.45
2009	1.10 (0.48-2.54)	0.82	0.80 (0.50-1.27)	0.35
2010	1.36 (0.60-3.08)	0.46	1.23 (0.79-1.90)	0.36
2011	1.77 (0.81-3.88)	0.15	0.85 (0.54-1.35)	0.49
2012	1.17 (0.49-2.77)	0.73	0.94 (0.60-1.49)	0.80
2013	0.86 (0.33-2.25)	0.76	0.92 (0.57-1.47)	0.72

*Antiplatelet therapy excluded from the analysis of elective cases because of colinearity.
PCI=percutaneous coronary intervention, CABG=coronary artery bypass graft

Table 3: Significant predictors of hemorrhagic stroke outcome by type of PCI

Variables	Elective PCI	P	Non-elective PCI	P
Age	1.02 (0.98-1.06)	0.40	**1.03 (1.01-1.04)**	**0.003**
Female	**2.65 (1.13-6.24)**	**0.026**	**1.57 (1.06-2.31)**	**0.024**
Smoking status*		-		
Non-smoker	-		1.00 (ref)	-
Ex-smoker	-		1.07 (0.68-1.69)	0.77
Current smoker	-		0.83 (0.48-1.41)	0.48
Hypertension	0.87 (0.34-2.21)	0.78	1.16 (0.77-1.75)	0.48
Hypercholesterolemia	1.41 (0.54-3.72)	0.48	0.67 (0.45-1.02)	0.061
Diabetes	0.50 (0.14-1.73)	0.28	1.21 (0.75-1.94)	0.44
Previous myocardial infarction	0.64 (0.22-1.91)	0.43	0.90 (0.54-1.50)	0.68
Previous stroke	**4.07 (1.13-14.62)**	**0.031**	1.53 (0.76-3.10)	0.24
Peripheral vascular disease	1.26 (0.27-5.82)	0.76	1.58 (0.79-3.15)	0.20
Renal disease	2.21 (0.28-17.17)	0.45	1.88 (0.89-3.99)	0.10
Previous PCI	2.06 (0.83-5.13)	0.12	**1.88 (1.08-3.29)**	**0.027**
Previous CABG	1.64 (0.70-3.87)	0.25	**0.61 (0.40-0.93)**	**0.020**
Cardiogenic shock	-	-	**2.34 (1.20-4.54)**	**0.012**
Receipt of ventilation	-	-	1.97 (0.97-3.98)	0.059
Circulatory support	-	-	**2.17 (1.11-4.27)**	**0.024**
Antiplatelet therapy*		-		
Clopidogrel	-		1.00 (ref)	-
Prasugrel	-		0.63 (0.21-1.87)	0.40
Ticagrelor	-		0.28 (0.03-2.23)	0.23
Warfarin use	3.15 (0.41-24.06)	0.27	2.46 (0.77-7.87)	0.13
Glycoprotein IIb/IIIa inhibitor use	**4.83 (1.95-12.01)**	**0.001**	0.96 (0.64-1.44)	0.86
Left main stem disease	**4.11 (1.21-13.97)**	**0.024**	1.12 (0.50-2.49)	0.79
Thrombectomy	-	-	0.97 (0.57-1.64)	0.90
Recent thrombolysis	-	-	**3.91 (2.49-6.15)**	**<0.001**
STEMI	-	-	**3.44 (2.24-5.28)**	**<0.001**
Year				
2006	1.00 (ref)	-	1.00 (ref)	-
2007	0.66 (0.16-2.76)	0.56	0.92 (0.42-2.00)	0.83
2008	0.87 (0.23-3.31)	0.84	1.00 (0.47-2.11)	0.99
2009	0.67 (0.16-2.89)	0.59	1.08 (0.51-2.25)	0.85
2010	0.76 (0.17-3.32)	0.72	0.81 (0.37-1.77)	0.60
2011	0.53 (0.10-2.83)	0.45	**0.24 (0.09-0.68)**	**0.007**
2012	0.25 (0.03-2.24)	0.22	0.49 (0.20-1.18)	0.11
2013	0.25 (0.03-2.27)	0.22	0.54 (0.22-1.32)	0.18

Smoking status and antiplatelet was omitted from the elective analysis because it is a perfect predictor.

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

Table 4: Risk of adverse outcomes (MACE or 30-d mortality) among patients who had any stroke, ischemic stroke and hemorrhagic stroke by elective or non-elective procedures

	Crude rate for elective with stroke vs no stroke	OR Elective (ref-no stroke)	P	Crude rate for non-elective with stroke vs no stroke	OR non-elective (ref. no stroke)	p	OR Non-elective Cf. elective among those who developed stroke post PCI (ref. elective)	P
Both type								
-MACE	27/113 (24%) vs 2303/231664 (1%)	21.05 (13.25-33.44)	<0.001	165/592 (28%) vs 9363/328070 (3%)	6.25 (5.03-7.77)	<0.001	0.63 (0.35-1.15)	0.13
-30-d mortality	16/122 (13%) vs 757/227147 (0.3%)	37.90 (21.43-67.05)	<0.001	156/577 (27%) vs 10350/320878 (3%)	5.00 (3.96-6.31)	<0.001	1.24 (0.64-2.43)	0.52
Ischemic								
-MACE	23/91 (25%) vs 2303/231664 (1%)	25.13 (15.29-41.31)	<0.001	122/475 (26%) vs 9363/328070 (3%)	5.48 (4.27-7.04)	<0.001	0.44 (0.22-0.86)	0.016
-30-d mortality	6/90 (6.7%) vs 757/227147 (0.3%)	17.61 (7.51-41.33)	<0.001	99/466 (21%) vs 10350/320878 (3%)	3.11 (2.34-4.13)	<0.001	1.70 (0.64-4.53)	0.29
Hemorrhagic								
-MACE	4/22 (18%) vs 2303/231664 (1%)	8.67 (2.48-30.27)	0.001	43/117 (37%) vs 9363/328070 (3%)	10.00 (6.39-15.66)	<0.001	3.89 (0.65-23.19)	0.14
-30-d mortality	10/22 (45%) vs 757/227147 (0.3%)	175.24 (67.69-453.66)	<0.001	57/111 (51%) vs 10350/320878 (3%)	21.50 (13.81-33.46)	<0.001	1.30 (0.35-4.87)	0.70

Adjusted for age, female gender, smoking status, hypertension, hypercholesterolemia, diabetes, previous myocardial infarction, previous stroke, peripheral vascular disease, renal disease, valvular heart disease, previous percutaneous coronary intervention and previous coronary artery bypass graft, cardiogenic shock, receipt of ventilation and circulatory support, antiplatelet use, warfarin use, glycoprotein IIb/IIIa inhibitor use, thrombectomy use, left main stem disease, thrombolysis use, STEMI diagnosis and year of PCI adjusted.
MACE=major adverse cardiovascular event

SUPPLEMENTAL MATERIAL

Supplemental Methods

The variables included as potential confounders in multiple logistic regression models were age, sex, smoking status (never smoked, ex-smoker, current smoker), presence of diabetes, hypertension, hyperlipidemia, previous myocardial infarction (MI), previous stroke, peripheral vascular disease, renal disease, valvular heart disease, previous PCI, previous coronary artery bypass graft, cardiogenic shock, use of circulatory support, use of thrombectomy, left main stem PCI, use of glycoprotein IIb/IIIa inhibitor, oral antiplatelets (clopidogrel, prasugrel, ticagrelor), warfarin, use of thrombolytic agents, and year of procedure.

We used a step-wise modeling approach to better understand the associations and the following models were constructed; Model 1: unadjusted; Model 2: age, sex and smoking status adjusted; Model 3: as in model 2 and additional adjustment for hypertension, hypercholesterolemia, diabetes, previous myocardial infarction, previous stroke, peripheral vascular disease, renal disease, valvular heart disease, previous percutaneous coronary intervention and previous coronary artery bypass graft; Model 4: as in Model 3 with additional adjustment for cardiogenic shock, receipt of ventilation and circulatory support; Model 5: as in Model 4 plus adjustment for antiplatelet use, warfarin use, glycoprotein IIb/IIIa inhibitor use, thrombectomy use, left main stem disease, thrombolysis use, STEMI diagnosis and year of PCI. These results are presented in Supplementary Table 2 and Model 5 is presented in Table 4.

To account for baseline differences across stroke groups, multiple imputations with propensity score matching (*mi estimate: teffects psmatch* on Stata) was used to estimate the average treatment effect (ATE). The method was used to analyze two separate logistic treatment models (ischemic stroke vs. no stroke and any stroke vs. no stroke), calculating propensity scores for group membership. Analysis for hemorrhagic stroke vs. no stroke was

not possible because of too low propensity scores for many cases. Standard settings for the matching algorithm were used with a minimum of one neighbor requested for all observations and potential matches considered regardless of how dissimilar their propensity score. Tolerance for the overlap assumption was set to 10^{-5}. We excluded variables which were perfect predictors from the propensity matching analysis.

Supplementary Table I: Missing data table

Variable	Data available	Missing data	% missing
Age	560,439	0	0
Female	560,439	0	0
Smoking status	485,966	74,473	13
Hypertension	544,210	16,229	3
Hypercholesterolemia	544,210	16,229	3
Diabetes	529,247	31,192	6
Previous myocardial infarction	498,798	61,641	11
Previous stroke	544,210	16,229	3
Peripheral vascular disease	544,210	16,229	3
Renal disease	556,005	4,434	0.8
Valvular heart disease	544,210	16,229	3
Previous PCI	534,219	26,220	5
Previous CABG	560,439	0	0
Cardiogenic shock	517,569	42,870	8
Ventilated	462,794	97,645	17
Circulatory support	515,176	45,263	8
Antiplatelet therapy	417,266	143,173	26
Warfarin	516,457	43,982	8
Glycoprotein IIb/IIIa inhibitor	516,790	43,649	8
Thrombectomy	537,922	22,517	4
Left main stem disease	539,136	21,303	4
Recent thrombolysis	509,443	50,996	9
STEMI	560,439	0	0
MACE	560,439	0	0
Mortality at 30 days	548,714	11,725	2

PCI=percutaneous coronary intervention, CABG=coronary artery bypass graft, MACE=major adverse cardiovascular event

Supplementary Table II: Risk of adverse outcomes (MACE or 30-d mortality) among patients who had any stroke, ischemic stroke and hemorrhagic stroke by elective or non-elective procedures

	OR Elective (ref-no stroke)	P	OR non-elective (ref. no stroke)	p	OR Non-elective Cf. elective among those who developed stroke post PCI (ref. elective)	p
Both type						
-MACE						
Model 1	31.27 (20.25-48.27)	<0.001	13.15 (10.98-15.76)	<0.001	1.23 (0.77-1.97)	0.39
Model 2	29.35 (18.97-45.42)	<0.001	11.23 (9.34-13.51)	<0.001	1.20 (0.74-1.95)	0.46
Model 3	29.58 (19.07-45.90)	<0.001	10.87 (9.02-13.10)	<0.001	1.14 (0.69-1.89)	0.61
Model 4	29.17 (18.64-45.66)	<0.001	7.47 (6.00-9.29)	<0.001	0.84 (0.49-1.42)	0.51
Model 5	21.05 (13.25-33.44)	<0.001	6.25 (5.03-7.77)	<0.001	0.63 (0.35-1.15)	0.13
-30-d mortality*						
Model 1	49.84 (29.22-85.02)	<0.001	11.12 (9.24-13.37)	<0.001	2.22 (1.27-3.89)	0.005
Model 2	45.97 (26.58-79.50)	<0.001	9.26 (7.64-11.21)	<0.001	2.06 (1.16-3.67)	0.014
Model 3	46.97 (26.91-81.99)	<0.001	9.12 (7.51-11.07)	<0.001	1.98 (1.09-3.58)	0.024
Model 4	46.21 (26.33-81.09)	<0.001	6.05 (4.79-7.64)	<0.001	1.54 (0.84-2.83)	0.16
Model 5	37.90 (21.43-67.05)	<0.001	5.00 (3.96-6.31)	<0.001	1.24 (0.64-2.43)	0.52
Ischemic						
-MACE						
Model 1	33.69 (20.96-51.14)	<0.001	11.76 (9.57-14.47)	<0.001	1.02 (0.61-1.71)	0.94
Model 2	31.70 (19.68-51.09)	<0.001	9.94 (8.05-12.27)	<0.001	1.00 (0.58-1.71)	1.00
Model 3	32.18 (19.93-51.96)	<0.001	9.72 (7.85-12.02)	<0.001	0.88 (0.50-1.54)	0.66
Model 4	33.94 (21.03-54.78)	<0.001	6.57 (5.11-8.43)	<0.001	0.61 (0.34-1.09)	0.094
Model 5	25.13 (15.29-41.31)	<0.001	5.48 (4.27-7.04)	<0.001	0.44 (0.22-0.86)	0.016
-30-d mortality						
Model 1	21.36 (9.30-49.05)	<0.001	8.09 (6.48-10.11)	<0.001	3.78 (1.60-8.90)	0.002
Model 2	19.21 (8.27-44.63)	<0.001	6.53 (5.19-8.22)	<0.001	3.25 (1.36-7.78)	0.008
Model 3	19.73 (8.45-46.05)	<0.001	6.46 (5.12-8.16)	<0.001	2.82 (1.16-6.84)	0.022

Model 4	21.18 (9.08-49.38)	<0.001	3.76 (2.82-5.00)	<0.001	2.04 (0.83-5.05)	0.12
Model 5	17.61 (7.51-41.33)	<0.001	3.11 (2.34-4.13)	<0.001	1.70 (0.64-4.53)	0.29
Hemorrhagic						
-MACE						
Model 1	22.13 (7.48-65.44)	<0.001	19.78 (13.58-28.82)	<0.001	2.61 (0.83-8.23)	0.10
Model 2	20.59 (6.94-61.11)	<0.001	17.60 (11.99-25.83)	<0.001	2.81 (0.81-8.75)	0.10
Model 3	20.04 (6.67-60.23)	<0.001	16.36 (11.11-24.10)	<0.001	3.63 (0.92-14.34)	0.066
Model 4	12.97 (3.69-45.57)	<0.001	11.93 (7.60-18.74)	<0.001	3.99 (0.89-17.88)	0.070
Model 5	8.67 (2.48-30.27)	0.001	10.00 (6.39-15.66)	<0.001	3.89 (0.65-23.19)	0.14
-30-d mortality						
Model 1	249.22 (107.35-578.57)	<0.001	31.67 (21.82-45.97)	<0.001	1.27 (0.51-3.17)	0.61
Model 2	255.77 (105.52-619.98)	<0.001	29.69 (20.13-43.81)	<0.001	1.37 (0.51-3.66)	0.53
Model 3	278.98 (113.23-687.36)	<0.001	28.48 (19.23-42.18)	<0.001	1.73 (0.60-5.04)	0.31
Model 4	221.14 (87.67-557.80)	<0.001	26.24 (16.90-40.74)	<0.001	1.49 (0.49-4.59)	0.49
Model 5	175.24 (67.69-453.66)	<0.001	21.50 (13.81-33.46)	<0.001	1.30 (0.35-4.87)	0.70

Model 1: unadjusted.
Model 2: age, female gender and smoking status adjusted.
Model 3: Model 2 + hypertension, hypercholesterolemia, diabetes, previous myocardial infarction, previous stroke, peripheral vascular disease, renal disease, valvular heart disease, previous percutaneous coronary intervention and previous coronary artery bypass graft adjusted.
Model 4: Model 3 + cardiogenic shock, receipt of ventilation and circulatory support adjusted.
Model 5: Model 4 + antiplatelet use, warfarin use, glycoprotein IIb/IIIa inhibitor use, thrombectomy use, left main stem disease, thrombolysis use, STEMI diagnosis and year of PCI adjusted.
MACE=major adverse cardiovascular event

Supplementary Table III: Propensity score matched results for risk of in-hospital MACE and 30-day mortality for ischemic stroke and any stroke

Analysis	Method	Group	Coefficient	95% CI		p-value
In-hospital MACE	Propensity score matching, ATE	No stroke in elective patient	Reference			
		Ischemic stroke in elective patient	0.1648	0.0632	0.2664	0.002
	Propensity score matching, ATE	No stroke in non-elective patient	Reference			
		Ischemic stroke in non-elective patient	0.1063	0.0603	0.1523	<0.001
	Propensity score matching, ATE	No stroke in elective patient	Reference			
		Any stroke in elective patient	0.1346	0.0663	0.2028	<0.001
	Propensity score matching, ATE	No stroke in non-elective patient	Reference			
		Any stroke in non-elective patient	0.1216	0.0809	0.1623	<0.001
30-day mortality	Propensity score matching, ATE	No stroke in elective patient	Reference			
		Ischemic stroke in elective patient	0.0321	0.0001	0.0640	0.049
	Propensity score matching, ATE	No stroke in non-elective patient	Reference			
		Ischemic stroke in non-elective patient	0.0703	0.0331	0.1076	<0.001
	Propensity score matching, ATE	No stroke in elective patient	Reference			
		Any stroke in elective patient	0.0770	-0.0066	0.1606	0.069
	Propensity score matching, ATE	No stroke in non-elective patient	Reference			
		Any stroke in non-elective patient	0.1141	0.0732	0.1549	<0.001

MACE=major adverse cardiovascular event, ATE=average treatment effect