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Original Article

Routine aspiration thrombectomy is associated with increased stroke rates during primary percutaneous coronary intervention for myocardial infarction

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Abstract: Background: Recent studies have suggested that the routine use of aspiration thrombectomy catheters during primary percutaneous coronary intervention (PCI) do not result in improved mortality and may be associated with an increased stroke rate. This study sought to investigate this hypothesis. Methods: This was an observational study analysing data from a prospective database of 6366 patients undergoing primary PCI between August 2003 and May 2015 at a UK cardiac centre. Patients' details were collected from the hospital electronic database. Primary outcome was thirty-day stroke rates. Results: 3989 (62.7%) patients underwent PCI alone and 2,377 (37.3%) patients underwent PCI with adjuctive thrombus aspiration. PCI alone group had an older demographic (63 (± 14) years vs 60.7 (± 14)), a lower proportion of male participants 75% vs 79% (P=0.001) and cardiovascular risk factors such as hypertension 22.4% vs 25.3% (P=0.007), hypercholesterolemia 18.5% vs 22.6% (P<0.0001) and a history of smoking 33.5% vs 44.3% (P<0.0001). Thrombus aspiration was associated with a higher 30-day stroke rate [16 (0.7%) vs 11 (0.3%) (HR 2.51; 95% CI 1.03-6.08, P 0.03). Multivariate analysis suggested that this increased risk of stroke was maintained following adjustment for confounders (HR: 1.86; 95% CI 1.02-4.38). There was 379 deaths of which 114 (4.8%) were in the thrombus aspiration cohort vs 265 (6.6%) in PCI only cohort over the follow-up period (60 months). This resulted in a significantly lower rate of all-cause-mortality HR 0.70 (95% CI 0.52-0.94; P 0.02). There was no statistically significant difference in observed myocardial infarction rates HR 0.76 (95% CI 0.47-1.23; P 0.27) and the rates of unscheduled revascularisations HR 0.70 (95% CI 0.43-1.13; P 0.14) between the two groups. Conclusions: Our data series of STEMI patients, suggest that routine thrombus aspiration during primary PCI is associated with a significantly higher stroke, rate however, thrombus aspiration reduced mortality rate. This is consistent with current guidelines which don't recommend the routine use of thrombus aspiration for primary PCI. A possible mortality reduction in patients with high thrombus grades was seen which may warrant further study.

Keywords: Myocardial infarction, percutaneous coronary intervention, stroke, thrombectomy

Introduction

Primary Percutaneous Coronary Intervention (PCI) provides the most effective method of restoring coronary blood flow following ST segment elevation myocardial infarction (STEMI) and has been shown to improve cardiovascular outcomes [1-3]. However, the presence of high thrombus burden during angioplasty can cause distal clot embolization leading to poor microvascular flow and myocardial perfusion. This is demonstrated by poor ST segment resolution (STR), myocardial blush grade (MBG) and low TIMI score of 1-2 (thrombolysis in myocardial infarction) all of which are adverse prognostic markers [4].

Manual thrombus aspiration (e.g., export catheter) has been used as an adjunct to limit these microvascular complications of downstream clot migration with it previously considered routine prior to stent deployment during primary PCI. However, recent studies have created uncertainty and suggested possible harm such as increased stroke rates and no clear mortality benefit [5-12]. Trials such as INFUSE-AMI [13] and COCTAIL II [14] compared the benefit of utilising intracoronary abciximab and aspiration

thrombectomy by measuring infarct size using Cardiac magnetic resonance (CMR) imaging and did not demonstrate an advantage in patients who undergo manual thrombus aspiration. Recent larger studies such as TASTE [15] and TOTAL [7, 16] have not demonstrated a survival advantage. Therefore its use has been downgraded in the latest European society of cardiology and American heart association PCI guidelines [17, 18].

Stroke remains a rare complication of primary PCI [19, 20] and its incidence is reported in 1.3% following routine percutaneous coronary intervention following ST elevation myocardial infarction. More recently a large clinical trial reported a significantly higher stroke rate associated with patients undergoing manual thrombectomy compared to controlled groups (TOTAL). A meta-analysis with the largest clinical trials in this field (n=19,047 patients) failed to show an improvement in clinical outcomes from routine thrombus aspiration, however subgroup analysis of high-thrombus burden group did demonstrate an improvement in mortality at the cost of an increased stroke rate [8].

The aim of this study is to investigate the association between the routine use of thrombus aspiration and adverse outcomes including stroke, and all-cause mortality from a large tertiary centre database.

Method

Study design

This is a single centre observational cohort study of 6366 patients that underwent primary percutaneous coronary intervention (PCI) for ST elevation myocardial infarction (STEMI) in London, United Kingdom between August 2003 and May 2015. The aim of the study was to compare the outcomes of patients undergoing adjunctive thrombus aspiration vs primary PCI alone. Data was collected prospectively from London Heart Attack Centre based at St. Bartholomew's hospital. Data was collected prospectively into the British Cardiac Intervention Society (BCIS) registry as well as the local millennium system and the medical records were reviewed by study investigators. The review process was not anonymous.

The BCIS registry collects data from all patients who underwent PCI for STEMI. The database is updated at each admission and includes patient demographics, procedural timings, procedural details, in-patient investigations, treatment provided and clinical outcomes. The presenting symptoms, initial ECG findings as well as baseline patient data and demographic characteristics were assessed and recorded by the operating physicians. Patient demographics included age, gender, smoking status, left ventricular function, previous myocardial infarction (MI), previous revascularisation (PCI and Coronary Artery Bypass Grafting), indications for PCI, and New York Heart Association classification, as well as the presence of hypertension, diabetes mellitus, hypercholesterolemia, cardiogenic shock and pre-procedural cardiac arrest. The technical aspects of the PCI procedure were also recorded, as well as adverse outcomes, including complications up to the time of hospital discharge. Successful PCI results were defined as having a TIMI (thrombolysis in myocardial infarction) flow grade 3. The study outcomes included stroke, death, myocardial infarction and revascularisation. All-cause mortality was recorded from the UK Office of National Statistics (ONS).

Primary percutaneous coronary intervention pathway

The heart attack centre receives patients with ST segment elevation myocardial infarction from the northeast of London in an unselected manner. This also includes patient with cardiogenic shock and post cardiac arrest, intubated and ventilated patients. All patients admitted are taken to the cardiac catherisation laboratory under the supervision of a consultant cardiologist with the service operating 24 hours a day, 7 days a week. Outside of normal working hours an "on-call" team consists of an interventional cardiologist, senior specialist registrar, two cardiac catheterization nurses, a cardiac physiologist and a radiographer. The primary PCI service performance has been validated to operate on a 24 hourly basis, 7 days a week with uniform performance regardless of the time [21].

Primary PCI was performed by the interventional cardiologist. Standard primary PCI protocol includes pre-loading with aspirin 300 mg, clopidogrel 600 g, and Aspiration thrombectomy was available at the operator's discretion. The degree of coronary artery disease was classi-

fied visually by severity of luminal narrowing (0%, 1-49% (mild), 50-74% (moderate), 75-99% (severe), or 100% occlusion) and by vessel effected (e.g. Left anterior descending). In select cases, a Glycoprotein IIb/IIIa inhibitor such as eptifibitide was used.

Inclusion and exclusion criteria

All patients that qualified the primary PCI strategy, i.e. presenting within 12 hours of the onset of signs and symptoms of a STEMI were included. This includes a consistent history, ECG showing >1 mm ST segment elevation in two or more contiguous limb leads or >2 mm ST segment elevation in two or more contiguous precordial leads or new left bundle branch block. Patients who were unable to undergo immediate coronary angiography due to clinical status or who had delayed angiography and percutaneous intervention as well as those that underwent intravenous system thrombolytic therapy or surgical revascularisation were not included in the analysis.

Clinical outcomes

The primary end point was incidence of stroke within 30 days of procedure. The diagnosis was based on clinical grounds on history and computer tomography imaging. The secondary outcome of the study is composite all-cause mortality, myocardial infarction and unscheduled revascularisation. We hypothesised that thrombus aspiration use was associated with a higher risk of stroke and increased mortality.

Ethics

The data collected was part of a mandatory national cardiac audit. All patient identifiable fields were removed prior to analysis. Therefore local ethics committee approval was not required.

Statistical method

Patient demographics and follow-up data were collected at the initial consultation and by reviewing medical records. Statistical analysis was carried out using GraphPad Prism 7.0 and SPSS (Statistical package for social services, version 23, Hampshire, UK). Categorical variables were compared using cross tabulations and analysed for statistical significance using Pearson's Chi squared test or independent T test. For the purpose of statistical analysis, the study population was divided into two groups: PCI only group compared with PCI with adjunct thrombus aspiration group. The characteristics of the patients were compared using independent T test (for comparing means) and Pearson's Chi squared test (to compare frequency of distribution). A p value bellow 0.05 was deemed a statistically significant result. Primary outcome was stroke incidence. The secondary outcomes were all cause mortality, major adverse cardiac events including myocardial infarction and unscheduled revascularisation. Binary logistic regression was used to compute the effects of intervention on outcomes and to estimate the hazard ratio for the effect of thrombus aspiration on primary outcome. Kaplan-Meier curve was used to represent survival analysis. The time was measured from the date of admission to primary or secondary outcome (all-cause mortality). A number of co-variates were included in the model, including age, gender, diabetes, hypertension, hypercholesterolaemia, previous PCI, previous MI, pre-procedure TIMI flow, glycoprotein IIb/IIIA use, presence of cardiogenic shock and method of vascular access.

Results

A total of 6366 patients presenting with a STEMI to a London tertiary cardiology centre between August 2003 to May 2015 were included in the analysis. Of the total cohort 3989 (62.7%) patients underwent PCI alone while 2,377 (37.3%) patients underwent adjunctive thrombus aspiration.

Rates of thrombus aspiration and time

Thrombectomy utilisation rates changed over the study period, with the percentage of patients undergoing thrombectomy by year between 2003 and 2015 shown in **Figure 1**. Although the percentage of patients who underwent thrombectomy increased initially as reflected by guidelines and publication of supportive data (i.e. TAPAS), there was a gradual decline in utilisation rates following the publication of the large TASTE Study.

Baseline characteristics

The baseline characteristics between the two groups were compared and illustrated in **Table**

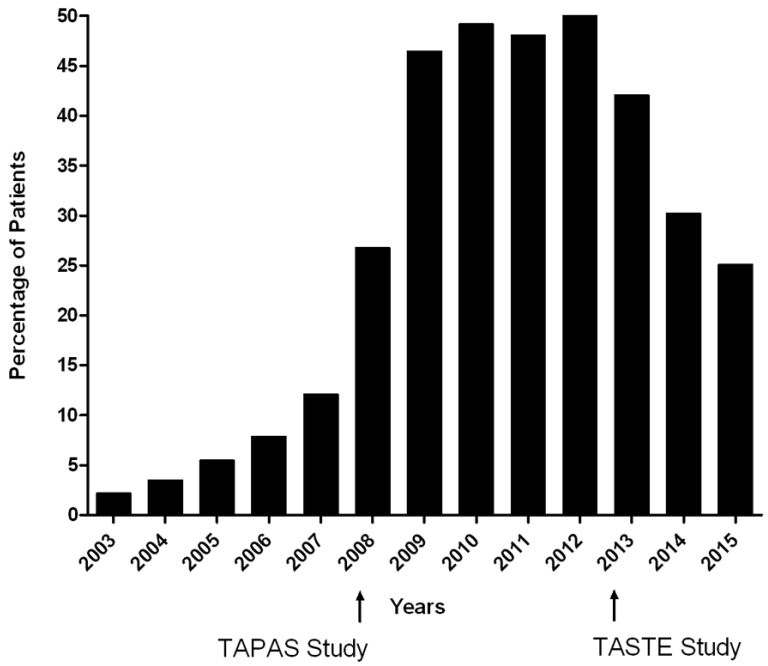

Figure 1. Percentage of patients undergoing thrombectomy before PPCI from 2003 to 2015. The bar graph shows the percentage of patients undergoing thrombectomy before PPCI from 2003 to 2015. PPCI = primary percutaneous coronary intervention.

1. Between the PCI group vs Aspiration thrombectomy groups the mean ages were significantly different with higher ages seen in the PCI alone group (63 (± 14) years vs 60.7 (± 14)). The thrombectomy group had a higher proportion of male participants 75% vs 79% (P=0.001) and cardiovascular risk factors such as hypertension 22.4% vs 25.3% (P=0.007), hypercholesterolemia 18.5% vs 22.6% (P<0.0001) and a history of smoking 33.5% vs 44.3% (P<0.0001).

The time from symptom onset to index procedure differed between the groups, with PCI alone patients having a longer time to presentation (298 mins vs 247 mins; P 0.01) between the groups. Time from hospital admission to procedure times was similar between the groups (60 mins vs 65 mins; P 0.16).

Procedural characteristics

The intra-procedural characteristics are described in **Table 2**. The thrombus burden in the thrombus aspiration group was higher and therefore had a higher proportion of patients with TIMI 0 flow (52.9% vs 77.5%; P<0.0001).

The vast majority of interventions were done on the left anterior descending artery or right coronary artery and only a small proportion of interventions involved the left main stem. Patients undergoing thrombus aspiration were more likely to receive more stents and to have undergone multi-vessel intervention (10.3% vs 6.3%; P 0.001). The use of Glycoprotein IIb/IIIa inhibitors was lower in the PCI only group (82.9% vs 86.9%; P<0.0001). Similar procedural success rates were seen in the 2 groups.

Primary outcome-30-day stroke incidence: In total 27 stroke events occurred in the whole study cohort. The results of this as-treated analysis demonstrated a statistically significant difference between the two groups (**Table 3**). The cohort of patients that underwent aspiration thrombectomy demonstrated a statistically significant increased stroke rate compared to the PCI only cohort [16 (0.7%) vs 11 (0.3%) (P=0.03), hazard ratio (HR) 2.51; 95% confidence interval (CI) 1.03-6.08]. Multivariate analysis suggested that this increased risk of stroke was maintained following adjustment for confounders (HR: 1.86; 95% CI 1.02-4.38). **Table 4** analyses the other predictors of the primary outcome stroke.

Secondary outcomes: The secondary outcomes including all-cause-mortality, rate of myocardial infarction and unscheduled revascularization are shown in **Table 3**. Survival was estimated by the Kaplan-Meier method (**Figure 2**). There were 379 deaths of which 114 (4.8%) was in the thrombus aspiration cohort vs 265 (6.6%) in the PCI only cohort over the follow-up period (60 months). This resulted in a significantly lower rate of all-cause-mortality HR 0.70 (95% CI 0.52-0.94; P 0.02). There was no statistically significant difference in observed myocardial infarction rates HR 0.76 (95% CI 0.47-1.23; P 0.27) and the rates of unscheduled revascularisations HR 0.70 (95% CI 0.43-1.13; P 0.14) between the two groups.

High thrombus grade subgroup

The pre-procedure coronary blood flow was classified by the thrombolysis in myocardial

Table 1. Baseline characteristics of the comparator groups

		PCI Alone (n=3989)	Aspiration Thrombectomy (n=2377)	*p* value
Mean Age ± STD (Years)		63 (STD 14)	60.7 (STD 14)	<0.0001*
Gender	Male (%)	2961 (75)	1862 (79)	0.001
	Female (%)	991 (25)	501 (21)	0.001
Previous MI (%)		361 (9.0)	230 (9.7)	0.405
Previous CABG (%)		87 (2.2)	39 (1.6)	0.134
Previous PCI (%)		267 (6.7)	206 (8.7)	0.004
Diabetes (%)		496 (12.4)	315 (13.3)	0.344
Hypertension (%)		892 (22.4)	602 (25.3)	0.007
Hypercholesterolemia (%)		736 (18.5)	537 (22.6)	<0.0001
History of Smoking (%)		1338 (33.5)	1052 (44.3)	<0.0001
Card Shock (%)		247 (6.5)	167 (7.0)	0.446
Symptom onset to procedure time		298 mins (IQR 260 mins)	247 mins (IQR 185 mins)	0.01
Door to Balloon time		60 mins (IQR 40 mins)	65 mins (IQR 19 mins)	0.16
LV Function				0.001
Good LV (%)		1359 (50.1)	681 (44.5)	
Mild LV		367 (13.5)	201 (13.1)	
Moderate LV		685 (25.3)	451 (29.4)	
Severe LV		301 (11.1)	199 (13.0)	

*Independent sample T test to compare means.

Table 2. Percutaneous coronary intervention procedural characteristics and angiographic results

	PCI only	Aspiration Thrombectomy	*p* value
Access			0.001
Radial	1047 (42.1)	1211 (60.7)	
Femoral	1439 (57.9)	783 (29.3)	
Pre-procedure angiographic findings Baseline TIMI flow			<0.0001
0	615 (52.9)	1415 (77.5)	
1	78 (6.7)	98 (5.4)	
2	109 (9.4)	105 (5.7)	
3	361 (31)	208 (11.4)	
MI thrombus grade, n (%)			0.098
0, No thrombus present	49 (8.0)	82 (5.8)	
1, Possible thrombus present	71 (11.5)	142 (10.0)	
2, Definite thrombus present, <0.5 vessel diameter	26 (4.2)	55 (3.9)	
3, Definite thrombus present, 0.5-2.0 vessel diameters	76 (12.4)	197 (13.9)	
4, Definite thrombus present, >2.0 vessel diameters	87 (14.1)	221 (15.6)	
5, Total occlusion	234 (38.0)	512 (36.2)	
Procedure details			
Glycoprotein Iib/IIIa use	1955 (82.9%)	1558 (86.9%)	<0.0001
Number of stents			<0.0001
1	1203 (54.0)	1118 (61.3)	
2	658 (29.6)	495 (27.2)	
3	227 (10.2)	144 (7.9)	
≥4	138 (6.2)	66 (3.6)	
Total (n)	2226	1823	

Target treated			0.001
Culprit only	2141 (89.7)	1800 (93.7)	
Multivessel	251 (10.3)	122 (6.3)	
Vessel Intervened			0.001
LMS	8 (0.2)	5 (0.2)	
LAD	963 (24.1)	792 (33.3)	
LCx	247 (6.2)	198 (8.3)	
RCA	837 (21)	753 (31.3)	
Vein Graft intervention	57 (1.4)	43 (1.8)	
Post-procedure results			
TIMI flow			0.218
0	49 (2.4)	28 (1.5)	
1	20 (1)	21 (1.1)	
2	57 (2.8)	58 (3.1)	
3	1919 (93.8)	1735 (94.2)	
Total (n)	2045	1842	
Coronary Stenting			<0.0001
Bare metal stents (BMS)	1165 (58.7%)	647 (45.5%)	
Drug eluting stents (DES)	820 (41.3%)	766 (53.8%)	
Both BMS and DES	26 (1.3%)	10 (0.7%)	

Table 3. Primary and secondary outcomes

Outcome	PCI Alone	Thrombectomy	HR (95% Confidence Interval)	*p* value
Primary outcome 30 day stroke	11 (0.3)	16 (0.7)	2.51 (1.03-6.08)	0.03
All-cause mortality	265 (6.6)	114 (4.8)	0.70 (0.52-0.94)	0.02
Myocardial infarction	78 (5.0)	30 (3.9)	0.76 (0.47-1.23)	0.27
Unscheduled revascularisation	92 (5.9)	27 (4.0)	0.70 (0.43-1.13)	0.14

Table 4. Other predictors of primary outcome stroke

Subgroup	Hazard Ratio (95% Confidence interval)	*P* value
Patient Characteristics		
Age	1.15 (1.05-2.18)	0.02
Diabetes	0.58 (0.17-2.01)	0.39
Hypertension	1.71 (0.69-4.25)	0.25
Hypercholestrolaemia	1.70 (0.68-4.29)	0.26
Previous Myocardial infarction	0.80 (0.16-3.94)	0.79
Previous PCI	1.39 (0.28-6.87)	0.69
Smoking history	0.87 (0.38-2.00)	0.74
TIMI flow pre-procedure		
TIMI 0-1	3.26 (0.76-14.10)	0.11
TIMI 2-3	0.31 (0.07-1.32)	0.11
Culprit only intervention	0.46 (0.16-1.36)	0.16
Multivessel intervention	2.15 (0.73-6.31)	
Use of glycoprotein iib/iiia inhibitor	0.91 (0.31-2.66)	0.86
Type of arterial access		
Radial	1.06 (0.50-2.26)	0.88
Femoral	0.94 (0.44-2.01)	

infarction grading (TIMI). A high thrombus as defined by pre-procedure TIMI thrombus grade of 0 (defined as absence of antegrade flow) or 1 (faint antegrade flow beyond occlusion). Within this subgroup analysis, use of aspiration thrombectomy was associated with an increased rate of stroke (HR 1.63, 95% CI 1.05-3.89), but an all-cause mortality benefit (HR 0.86, 95% CI 0.76-0.96) after adjusting for the same confounding variables described above, suggesting that despite the increased risk of stroke a mortality benefit is still seen.

Discussion

In this observational study of 6366 patients from a large heart attack centre, we report the primary and

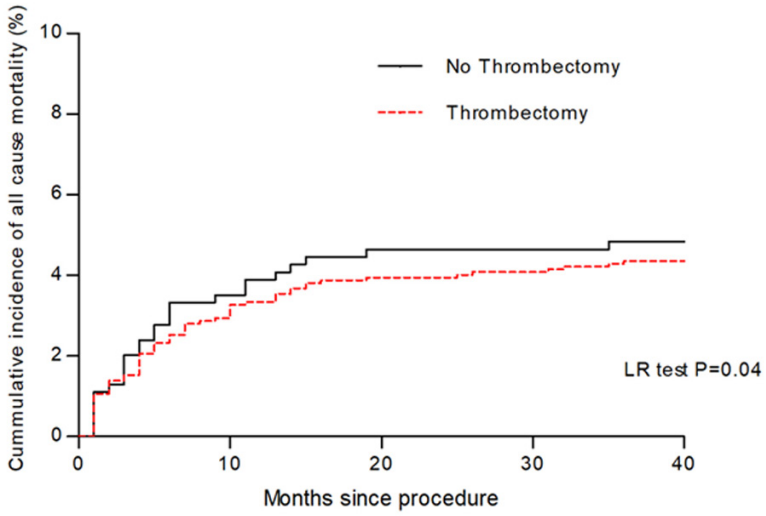

Figure 2. Kaplan-Meier Estimates for All-Cause Mortality at 36 months for the two treatment strategies: PCI with thrombectomy vs PCI alone group.

secondary outcomes of patients undergoing thrombus aspiration as an adjunct to PCI. There was a significantly increased rate of stroke observed in the cohort that underwent aspiration thrombectomy compared to PCI alone with hazard ratio 2.51; 95% confidence interval 1.03-6.08. The post hoc analysis also demonstrated a statistically significant result which identifies the primary outcome is consistent with the contemporary evidence in this field including some of the more recent trials. The 2.51 fold increase in event rates, cautions against the routine utilization of thrombectomy devices in coronary intervention. The primary outcome of 30 day stroke rates is a better reflection of the events related to intervention therefore our investigators did not arrange longer follow up. The mechanism of stroke being thromboembolic during or shortly after procedure.

The BCIS registry has captured a large study population in a busy tertiary cardiology center. Cohort size is comparable to other large studies looking at the outcomes related to manual thrombus aspiration, namely TASTE (n=7244) and TOTAL (n=10,732). The two cohorts had similar baseline characteristics however the thrombectomy group had a higher comorbidity burden with higher proportion of GP IIb/IIIa inhibitor use, higher rates of patients with a prior history of PCI, hypertension, hypercholesterolemia and prior smoking history. The overall study groups had equal response times to symptom onset. The time from symptom onset to balloon times as well as "door to balloon" times between the two groups were similar.

Consistent with data from meta-analyses of large RCTs [8], we observed a small overall mortality benefit with the use of routine adjunctive thrombus aspiration. The subgroup of patients with high thrombus burden also demonstrated a mortality benefit from thrombus aspiration. This would suggest that use of thrombus aspiration despite lowering morality comes at a cost of stroke morbidity. Possible improvements in technology or meticulous use of catheters (i.e. flushing, guide engagement) could be important or helpful in reducing the stroke risk if such devices are required as an adjunct to PCI. It is important to acknowledge that larger blinded trials have not shown a survival benefit in thrombus aspiration.

Complexity of intervention was not associated with an increased stroke risk since patients that underwent culprit only intervention and multivessel intervention did not show a statically significant stroke risk. Further subgroup analysis also did not demonstrate a treatment benefit of preventing further major adverse cardiovascular events such as recurrent myocardial infarction or unscheduled revascularization. Therefore adjunct thrombectomy was not necessary to modify the MACE risk. The use of GP IIb/IIIa inhibitors further negated the need for thrombectomy use as it favored the PCI only arm.

Study limitations

The main limitation to this study is the study design being a retrospective study that does add selection bias. There are a number of operators which select the patient's to either undergo thrombectomy or PCI alone. However given that thrombectomy is primarily utilized in the cohort of patient's with a high thrombus burden does allow appropriate patient' selection and is

much more of a realistic model as it measures the benefit/risk of selective thrombectomy vs PCI alone.

Conclusion

In conclusion patients who were treated for STEMI that underwent aspiration thrombectomy along with standard PCI had a statistically significant increased incidence of stroke compared to those who had PCI alone. There was also an overall survival benefit demonstrated with thrombus aspiration, particularly in the high-thrombus burden cohort which justifies its utilisation in select cases. This is consistent with current guidelines which don't recommend the routine use of thrombus aspiration for primary PCI.

Disclosure of conflict of interest

None.

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