New insights in management and prognosis in acute myocardial infarction

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Impact of thrombus burden in ST-segment elevation myocardial infarction patients

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Abstract

Objectives

We aimed to determine whether the burden of angiographically observed thrombus is associated with impaired myocardial reperfusion and all-cause mortality in patients with ST-segment Elevation Myocardial Infarction (STEMI). In a sub-analysis, we investigated the effect of thrombus aspiration in patients with large and with small thrombus burden.

Background

Limited data is available regarding the impact of thrombus burden on myocardial reperfusion and mortality in STEMI patients.

Methods

Of all consecutive STEMI patients treated with primary percutaneous coronary intervention between January 2004 and April 2010 we analyzed the coronary angiograms and collected mortality up to June 2014.

Results

Of the 2969 patients included, 68% had large (Thrombolysis In Myocardial Infarction thrombus score 4 or 5) and 32% small thrombus burden. Myocardial Blush Grade (MBG) 0/1 and 1-year mortality were higher in patients with large compared to patients with small thrombus burden (34% vs. 21% p<0.001 and 9.2% vs. 6.7% p=0.017). The presence of MBG 0/1 was lower when thrombus aspiration was performed, irrespective of whether the visible thrombus burden was large (31% vs. 38%, p=0.001) or small (18% vs. 25%, p=0.017).

Conclusions

Large thrombus burden is associated with impaired myocardial perfusion and 1-year mortality in STEMI patients. Irrespective of thrombus burden visible on angiography, thrombus aspiration is related to improved MBG.

Introduction

A large proportion of patients with ST-segment Elevation Myocardial Infarction (STEMI) have impaired myocardial perfusion despite a patent epicardial vessel after primary Percutaneous Coronary Intervention (PCI).[1,2] Distal embolization visible at angiography leads to worse outcomes and is associated with larger thrombus burden.[3,4] However, the high incidence of impaired myocardial perfusion cannot be explained by the relatively low incidence of angiographically visible distal embolization.[4,5] Impaired myocardial perfusion is assumed to be caused by, angiographically undetectable, microembolization and microvascular occlusion.[6,7] Nevertheless, whether myocardial perfusion caused by microembolization is also related to angiographically visible thrombus burden remains to be established.[8] Also whether the potential beneficial effects of thrombus aspiration on myocardial perfusion might be associated with angiographically visible thrombus burden remains unclear.[9-14] In this study, we sought to determine whether angiographically visible thrombus burden is associated with impaired myocardial perfusion and mortality in patients presenting with STEMI. Furthermore, we evaluated whether the beneficial effects of thrombus aspiration are depending on thrombus burden.

Methods

Study population and design

All consecutive STEMI patients treated with primary PCI at the University Medical Center Groningen in the Netherlands were included in our database. For this retrospective study, we analyzed data of STEMI patients admitted from January 2004 to April 2010. The criteria for STEMI were the following; ST-segment elevation of >0.1mV in ≥2 leads on the electrocardiogram, and onset of symptoms less than 12 hours or less than 24 hours with persisting symptoms due to ongoing ischemia. The criterion for primary PCI was successful crossing of the culprit lesion with a guidewire. From January 2004 until December 2004, STEMI patients were treated with conventional PCI (mainly balloon angioplasty followed by stent implantation). From January 2005 until December 2006, conventional PCI and thrombus aspiration followed by stent implantation were randomly performed in the context of TAPAS (Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarction Study).[10,15] Manual thrombus aspiration became the preferred treatment since December 2006, but the choice of procedure was left to the discretion of the operator. Acute pharmacotherapy was according to current international guidelines, including heparin, aspirin, clopidogrel and the glycoprotein IIb/IIa inhibitor abciximab.[16,17] All coronary angiograms were analyzed by either an independent core laboratory or by two experienced observers blinded to all clinical data.

Thrombus burden

Patients were included when thrombus burden was assessable on the angiogram before PCI. Thrombus burden was graded from 0 to 5 according to the Thrombolysis In Myocardial Infarction (TIMI) thrombus grade.[18] The definitions are as follows; TIMI thrombus grade 0, no angiographic characteristics of thrombus; grade 1, possible thrombus with reduced contrast density, haziness, irregular lesion contour or smooth convex 'meniscus' at the site of total occlusion suggestive but not diagnostic of thrombus; grade 2, definitive thrombus with greatest dimension ≤1/2 vessel diameter; grade 3, definitive thrombus with greatest dimension >1/2 but <2 vessel diameters; grade 4, definitive thrombus with greatest dimension ≥2 vessel diameters and grade 5, total occlusion. In this study, small thrombus burden was defined as TIMI thrombus grade ≤3 and large thrombus burden as TIMI thrombus grade ≥4. When assessable, thrombus burden was also graded after the first intervention: thrombus aspiration or balloon angioplasty.

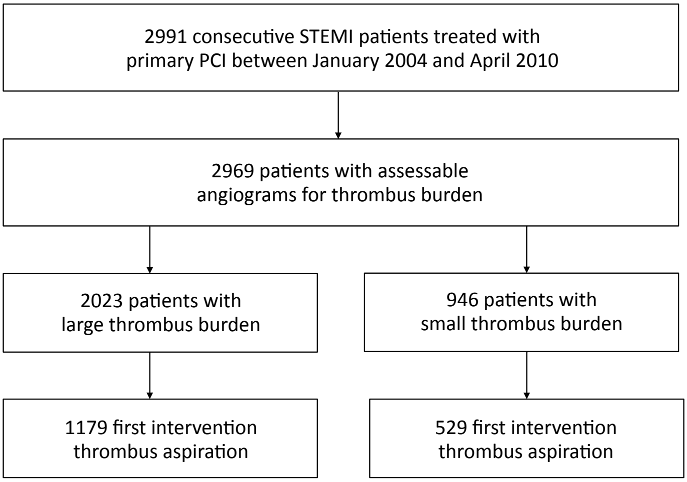
Definitions

Myocardial Blush Grade (MBG) was determined by the contrast density of the myocardial region of the infarct-related artery compared to the myocardial regions of non-infarct-related arteries. MBG was classified as MBG 0, no myocardial blush or persisting blush (staining); MBG 1, minimal myocardial blush; MBG 2, moderate myocardial blush or MBG 3, normal myocardial blush.[19] Impaired myocardial perfusion is defined as a MBG of 0 or 1. TIMI flow grade was classified as previously described.[20] Distal embolization was defined as angiographically visible filling defect and/or abrupt cut-off of the vessel distal to the culprit lesion.[6] ST-segment resolution was defined as more than 70% resolution of the ST-segment deviation on the electrocardiogram at presentation compared to the electrocardiogram at 30 to 60 minutes after primary PCI.[21] Thrombus aspiration was classified as effective when macroscopic atherothrombotic material was identified in the retrieved aspirate. In May 2014 mortality data was collected using the municipal civil registry, which contains completeness of vital status of all residents registered in The Netherlands.

Statistical analysis

Normally distributed continuous variables are presented as mean with standard deviation (SD) and were compared using a two-tailed Student's t-test. Skewed distributed continuous variables are presented as median with interquartile range (IQR) and were compared using a Mann Whitney U test. Categorical variables are presented as number and percentage and were compared using the χ^2 test or Fisher's exact test. Kaplan Meier curves were used to determine survival and differences were analyzed using the log-rank test. Statistical significance was defined as a two-sided p-value of less than 0.05. Statistical analysis was performed using SPSS software version 22.0 (Chicago, USA).

Figure 1 | Flow chart



STEMI patients were classified based on their thrombus burden observed angiographically and whether they were treated with thrombus aspiration as first intervention.
STEMI: ST-segment Elevation Myocardial Infarction.

Results

Large versus small thrombus burden

A total of 2991 patients presenting with STEMI were treated in our hospital with primary PCI. Of 2969 (99%) patients in whom the thrombus burden could be assessed on the coronary angiogram, 2023 (68%) patients had large thrombus burden and 946 (32%) patients had small thrombus burden (Figure 1). At baseline, patients with large thrombus burden had less diabetes mellitus, longer median ischemic time, more frequent the right coronary artery as culprit and more frequent an impaired TIMI flow (Table 1).

The impact of thrombus burden on angiographic, electrocardiographic and clinical outcomes is shown in Table 2. Angiographically visible distal embolization after PCI was seen more often in patients with large versus patients with small thrombus burden (15% versus 5%, p<0.001). MBG could be assessed in 2775 (93%) patients. Impaired myocardial perfusion was significantly higher in patients with large versus patients with small thrombus burden (34% versus 21%, p<0.001) (Table 2 and Figure 2). TIMI flow grade 3 after PCI was also lower in patients with large thrombus burden. Even in patients with TIMI flow grade 3 after PCI, the incidence of impaired myocardial perfusion was higher in patients with large compared

Table 1 | Baseline characteristics of patients with large versus with small thrombus burden in STEMI cohort

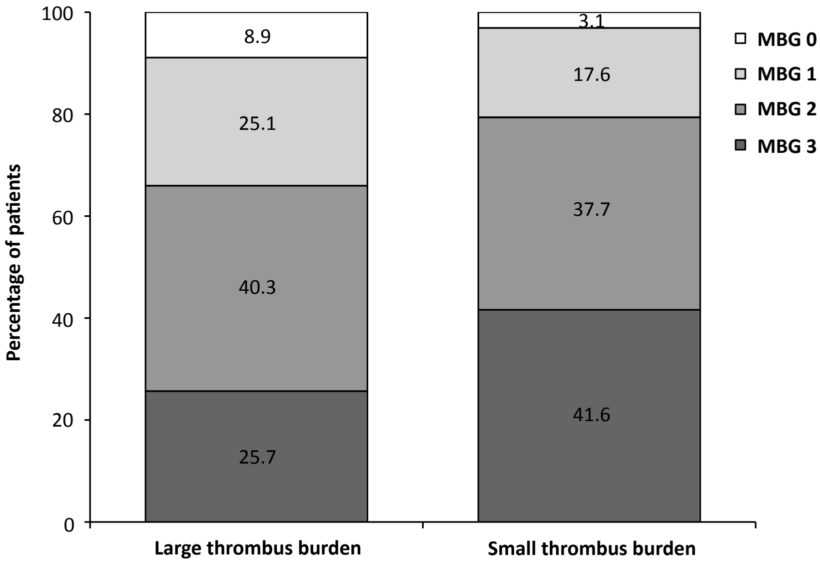
	Large thrombus burden n=2023	Small thrombus burden n=946	p-value
General			
Age, years	64±13	64±13	0.942
Male sex	1467 (73)	660 (70)	0.122
History			
Hypertension	723 (40)	333 (38)	0.358
Diabetes mellitus	219 (11)	129 (14)	0.032
Hypercholesterolemia	499 (30)	232 (28)	0.478
Myocardial infarction	181 (9)	97 (11)	0.308
PCI	161 (8)	71 (8)	0.650
CABG	56 (3)	28 (3)	0.779
Current smoking	883 (50)	430 (51)	0.472
Body mass index, kg/m^2	27.0±4	26.7±4	0.071
Cardiovascular disease in family	811 (46)	391 (45)	0.795
Ischemic time, minutes	190 (135-300)	180 (130-270)	0.010
Angiographic			
Infarct-related artery			<0.001
Left anterior descending	807 (40)	468 (50)	
Circumflex	303 (15)	163 (17)	
Right coronary artery	875 (43)	284 (30)	
Other	38 (2)	31 (3)	
TIMI flow grade			<0.001
0 or 1	1781 (88)	85 (9)	
2 or 3	241 (12)	857 (91)	
Multivessel disease	1266 (63)	566 (60)	0.173
Procedural			
Administration of glycoprotein IIb/ IIIa inhibitor	1735 (86)	807 (85)	0.741
Thrombus aspiration	1179 (58)	529 (56)	0.225

Data are presented as mean±SD, median (IQR) or as number (%).
PCI: percutaneous coronary intervention, CABG: coronary artery bypass grafting, TIMI: Thrombolysis In Myocardial Infarction.

to patients with small thrombus burden (22% vs. 16%, p<0.001). Finally, the incidence of ST-segment resolution was lower in patients with large thrombus burden.

During the median follow-up time of 6.6 years (IQR 4.9-8.4), 21.7% of the 2969 patients died. All-cause 1-year mortality was higher in patients with large versus patients with small thrombus burden (9.2% versus 6.7%, logrank p=0.017). This difference disappeared during

Figure 2 | MBG related to large and small thrombus burden



MBG 0 or 1 was significantly higher in patients with large thrombus burden versus patients with small thrombus burden (p<0.001). MBG: Myocardial Blush Grade.

Table 2 | Outcome characteristics in STEMI cohort

	Large thrombus burden n=2023	Small thrombus burden n=946	p-value
Post procedural			
MBG			<0.001
0 or 1	646 (34)	181 (21)	
2 or 3	1252 (66)	696 (79)	
TIMI flow grade			<0.001
<3	414 (21)	81 (9)	
3	1602 (79)	856 (91)	
Visible thrombus	117 (6)	17 (2)	<0.001
Distal embolization	276 (15)	41 (5)	<0.001
Side branch occlusion	42 (2)	14 (1)	0.261
Electrocardiographic			
Complete ST-segment resolution*	623 (52)	434 (68)	<0.001
Follow-up			
30 days mortality	137 (6.8)	36 (3.8)	0.001
1-year mortality	187 (9.2)	63 (6.7)	0.018

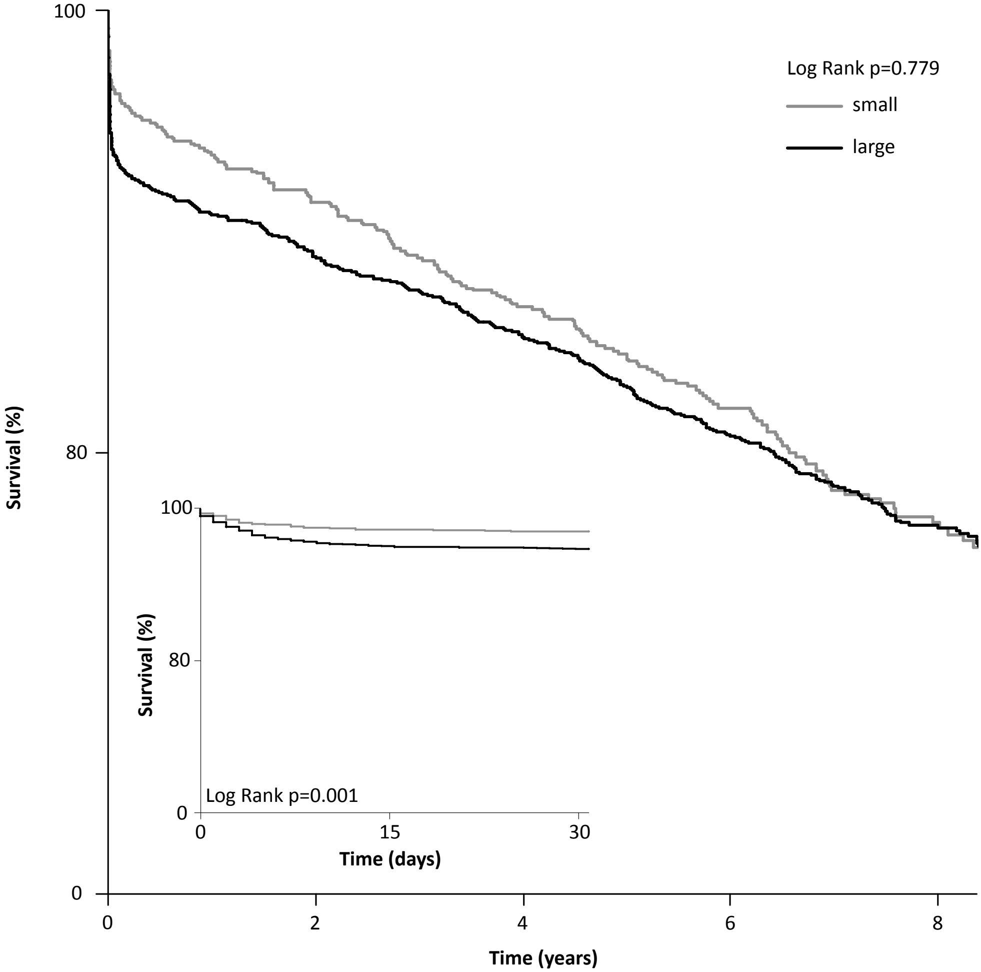
Data are presented as number (%).

* Data were available in 1205 patients with large and 641 patients with small thrombus burden.

MBG: Myocardial Blush Grade, TIMI: Thrombolysis In Myocardial Infarction.

long term follow-up; mortality of 21.6% in patients with large versus 21.7% in patients with small thrombus burden (logrank p=0.779) (Figure 3).

Figure 3 | Survival related to large and small thrombus burden

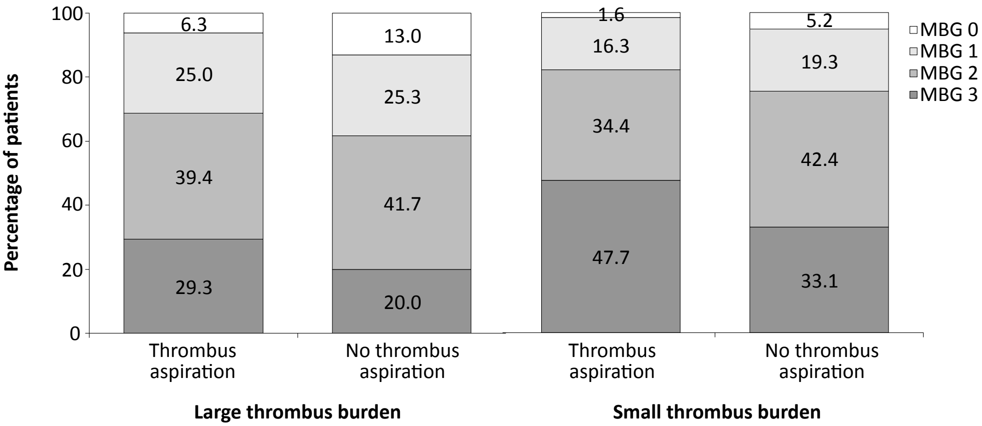


All-cause mortality rate was significantly higher in patients with large thrombus burden versus patients with small thrombus burden at 30-days and 1-year, but this disappeared during long term follow-up.

Impact of thrombus aspiration

Thrombus aspiration as first intervention was performed in 1708 patients; 1179 (58%) patients with large and 529 (56%) with small thrombus burden, respectively (Table 1). Overall, the incidence of impaired myocardial perfusion was significantly lower when thrombus aspiration was performed compared to when no thrombus aspiration was performed. When the effect of thrombus aspiration on myocardial perfusion was evaluated separately in patients with large and small thrombus burden this finding remained unchanged. In patients with large thrombus burden, impaired myocardial perfusion was seen in 31% of patients after thrombus aspiration and in 38% after conventional PCI (p=0.002). In patients with small thrombus burden this was seen in 18% of patients after thrombus aspiration and in 25% after conventional PCI (p=0.018) (Figure 4).

Figure 4 | Impact of thrombus aspiration on MBG related to large and small thrombus burden



MBG 0 or 1 was significantly lower when thrombus aspiration was performed, irrespective of whether patients had large or low thrombus burden (p<0.05).
MBG: Myocardial Blush Grade.

TIMI flow grade 3 after PCI was also more often seen when thrombus aspiration was performed compared to when no thrombus aspiration was performed in patients with large thrombus burden (85% versus 72%, p<0.001). However, in patients with small thrombus burden we did not observe a difference (93% versus 90%, p=0.130). There was no impact of thrombus aspiration on angiographically visible distal embolization compared to no thrombus aspiration as first intervention (in large thrombus burden 14% versus 16%, p=0.142, in small thrombus burden 6% versus 3% p=0.100). In 1535 (90%) patients, thrombus burden was prospectively scored before and after the first intervention. In 1408 (92%) of these patients with thrombus observed before PCI, reduction of thrombus burden with ≥1 TIMI thrombus grade was observed in 911 (87%) patients after thrombus aspiration and in 329 (90%) patients after balloon angioplasty as first intervention (p=0.211).

Retrieval of atherothrombotic burden

Retrieval of macroscopic aspirate was observed in 1241 of 1501 (83%) patients in who this was documented, after thrombus aspiration as first intervention. Thrombus aspiration was effective in 880 (86%) patients with large thrombus burden. In patients with small thrombus burden, thrombus aspiration was effective in 361 (75%) patients, of which 150 (71%) patients with no angiographically observed thrombus. Histopathological analysis was performed in 369 patients. Patients with large thrombus burden had larger retrieved aspirate and more erythrocyte components in the aspirate than patients with small thrombus burden (Table 3).

Table 3 | Retrieval of atherothrombotic burden

	Large thrombus burden n=2023	Small thrombus burden n=946	p-value
Retrieved aspirate*	880 (86)	361 (75)	<0.001
Histopathological analysis	244	125	
Size <0.5mm	110 (45)	90 (72)	<0.001
0.5-2.0mm	72 (30)	25 (20)	
>2.0mm	62 (25)	10 (8)	
Erythrocyte component	75 (31)	4 (3)	<0.001

Data are presented as number (%).
* Data were available in 1021 patients with large and 480 patients with small thrombus burden.

Discussion

Our observational study suggests that an angiographically visible large thrombus burden is associated with impaired myocardial perfusion, worse TIMI flow after PCI, more distal embolization, less complete ST-segment resolution and higher 1-year, but not long-term mortality. Reducing thrombus burden by thrombus aspiration is associated with improved myocardial perfusion, irrespective of thrombus burden.

Large versus small thrombus burden

We assume that the association between large thrombus burden and impaired myocardial perfusion can be explained by distal embolization. Impaired myocardial perfusion is thought to be mainly caused by embolization of particles of the atherothrombotic burden or vessel wall into the microvasculature.[7,22] This embolization can occur spontaneously or by iatrogenic mobilization as part of the thrombolysis or PCI.[7,22] Previous studies have suggested that large atherothrombotic burden before PCI increases the risk for embolization of atherothrombotic particles.[4,5] In this observational study, we indeed observed a higher incidence of distal embolization in patients with large thrombus burden. Since impaired myocardial perfusion is also observed in patients without distal embolization, angiographically undetectable microembolization is suspected to occur. The resulting microvascular obstruction cause micro occlusions of capillaries and consequently impair myocardial perfusion.[3,7,22]

Our data shows a higher 30-days and one year all-cause mortality in patients with large thrombus burden. Both impaired myocardial perfusion and large thrombus burden have been associated to worse outcomes.[19,23] Microvascular obstruction may play a role in this observation. Residual thrombus burden at the site of the lesion, present in more patients with large than in small thrombus burden, has been associated with restenosis and stent thrombosis as a response to its thrombogenic contents.[24,25] Restenosis and stent thrombosis may increase the rate of reinfarction and target-vessel revascularization, which may also explain the higher mortality rate. In our study the higher mortality rate can also be partly explained by the worse baseline characteristics in patients with large thrombus burden, including more often worse TIMI flow. The mortality difference diminished after long term follow up.

Impact of thrombus aspiration

In our data we observed that, irrespective of the thrombus burden visible on angiography, thrombus aspiration significantly improves myocardial perfusion in STEMI patients. By reducing the thrombus burden exposed to the lumen, thrombus aspiration is thought to decrease embolization of atherothrombotic material that might obstruct the distal (micro) vasculature.

The Thrombus Aspiration during Percutaneous Coronary Intervention in Acute Myocardial Infarction Study (TAPAS) trial demonstrated improved myocardial reperfusion after thrombus aspiration, irrespectively of angiographically observed thrombus using the definition of Mabin et al.[10,26] Other small randomised trials and early meta-analyses also showed positive findings of manual thrombus aspiration.[27,28] The more recent and largest trials to date observed no benefit on hard endpoints. The Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia (TASTE) trial revealed that manual thrombus aspiration did not reduce 30-days or 1-year mortality, also not in the subgroup of patients with large thrombus burden.[11,12] The trial of routine aspiration Thrombectomy with PCI versus PCI alone in patients with ST-elevation myocardial infarction undergoing primary PCI (TOTAL) confirmed these neutral findings on combined endpoint consisting of cardiovascular death, recurrent myocardial infarction, cardiogenic shock or severe heart failure at 6 months.[13,14] However, ST-segment resolution and distal embolization as reflectors of myocardial reperfusion were improved after using thrombus aspiration. No difference in outcome was found in subgroup analysis based on the thrombus burden. Still bailout thrombus aspiration was performed in 7% of patients after predilatation or after stent deployment. Furthermore, the lower rate of GP IIa/IIIb inhibitor administration in the thrombus aspiration group may have influenced the thrombus burden. In conclusion, these trials including almost 19,000 patients do not support routine use of manual thrombus aspiration. However, it is still unknown whether a strategy of selective thrombus aspiration in patients with large thrombus burden might be superior to no thrombus aspiration.

Limitations

The observations of our retrospective analysis should be interpreted with caution and only be considered as hypothesis-generating. A large randomized clinical trial could evaluate our observations whether a strategy of decreasing thrombus burden is beneficial in both small and large thrombus burden in STEMI patients. Results obtained in studies thus far are inconclusive. Secondly, our follow-up data is limited to all-cause mortality; no other hard endpoints were available.

Conclusion

This large observational study supports the assumption that large thrombus burden visible during angiography is associated with worse angiographic, electrocardiographic and clinical outcomes in patients with STEMI. Reducing the thrombus burden by thrombus aspiration might have a beneficial effect on myocardial perfusion irrespective of the amount of angiographically visible thrombus.

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