Presence of Older Thrombus Is an Independent Predictor of Long-Term Mortality in Patients With ST-Elevation Myocardial Infarction Treated With Thrombus Aspiration During Primary Percutaneous Coronary Intervention

Miranda C.A. Kramer, MD; Allard C. van der Wal, MD, PhD; Karel T. Koch, MD, PhD; Johanna P.H.M. Ploegmakers, BSc; René J. van der Schaaf, MD; José P.S. Henriques, MD, PhD; Jan Baan, Jr, MD, PhD; Saskia Z.H. Rittersma, MD, PhD; Marije M. Vis, MD; Jan J. Piek, MD, PhD; Jan G.P. Tijssen, PhD; Robbert J. de Winter, MD, PhD

Background—Routine thrombus aspiration is frequently used during primary percutaneous coronary intervention in patients with ST-elevation myocardial infarction to prevent distal embolization. Recently, evidence of clinical benefit was published. In 50% of the ST-elevation myocardial infarction patients with an onset of symptoms <12 hours before, thrombi were shown to be >1 day old. This observation illustrates that plaque rupture and coronary occlusion are significantly separated in time. In the present study, we correlate the presence of fresh versus older thrombus with long-term mortality.

Methods and Results—Thrombus aspiration was performed in 1315 patients treated with primary percutaneous coronary intervention with 3 devices (Rescue, Export, and Proxis). Aspirated material was fixed in formalin and processed for histopathology. If possible, thrombus age was classified as either fresh only (<1 day) or older (>1 day). We identified fresh thrombus in 552 patients and older thrombus in 372 patients. The cumulative Kaplan-Meier estimate of all-cause mortality at 4 years was significantly higher in patients with older thrombus (16.0%) compared with patients with fresh thrombus (7.4%), with a hazard ratio of 1.82 (95% confidence interval, 1.17 to 2.85; \(P=0.008\)). Multivariate analysis identified the presence of older thrombus, in addition to other established predictors, as an independent predictor (hazard ratio, 1.83; 95% confidence interval, 1.14 to 2.93; \(P=0.01\)) of long-term mortality.

Conclusion—Our study demonstrates that the presence of older thrombus, in addition to other established predictors, is an independent predictor of long-term mortality in patients with ST-elevation myocardial infarction treated with thrombus aspiration during primary percutaneous coronary intervention. (Circulation. 2008;118:1810-1816.)

Key Words: angioplasty ■ follow-up studies ■ myocardial infarction ■ pathology ■ thrombosis

Distal embolization of atherothrombotic material during primary percutaneous coronary intervention (PCI) for ST-elevation myocardial infarction (STEMI) is an important cause of (partly) unsuccessful reperfusion. A study showed that distal embolization was associated with a 5-fold increase in 5-year mortality.1 Many studies have been performed with adjunct thrombus aspiration and primary PCI to prevent distal embolization. Randomized clinical trials have shown that thrombus aspiration is associated with improved angiographic and electrocardiographic outcomes.2-7 Recently, the Thrombus Aspiration During Percutaneous Coronary Intervention in Acute Myocardial Infarction Study (TAPAS) trial showed clinical benefit in terms of improved event-free survival.8 Why it has been difficult to show clinical benefit in most randomized trials remains elusive. It may be the limited effectiveness of the devices; intracoronary material could be retrieved in only three quarters of the patients. In addition, the damage induced by large and bulky mechanical devices may outweigh the potential benefit of thrombus removal, but other factors may be as important.

Editorial p 1780
Clinical Perspective p 1816

We have shown previously that the aspirated thrombus fragments may be >12 hours old in STEMI patients with an onset of symptoms <12 hours before.9 In \(\approx 50\%\) of patients, the thrombus showed features of lytic changes (>24 hours to 5 days) and organization (>5 days). Pathology studies with...
sudden death victims that looked into the process of plaque instability and intracoronary thrombus formation have confirmed that plaque rupture and thrombus formation started days or even weeks before the (fatal) STEMI.10,11

To the best of our knowledge, the association between thrombus age and clinical outcome in patients with STEMI has not yet been studied. The aim of the present study is to correlate the presence of fresh versus older thrombus with long-term mortality in patients who underwent thrombus aspiration during primary PCI.

**Methods**

**Setting**

Our institution is a large referral hospital with an annual PCI volume of 2400 procedures, 600 of which are primary PCIs. Patients are eligible for primary PCI when they present with acute STEMI (≥2-mm ST elevation in ≥2 contiguous leads) with symptom duration of <12 hours. All interventions are done according to current standard guidelines for PCI. Thrombus aspiration has been part of the clinical routine in primary PCI since August 2001. Three different thrombectomy devices have been used: the 7F Rescue catheter (Boston Scientific/Scimed, Inc, Maple Grove, Minn), which became available in August 2001 and was mainly used until the end of 2004; the 6F Export aspiration catheter (Medtronic Vascular Inc, Santa Rosa, Calif), which became available in August 2004; and the 6/7F Proxis embolic protection device (St Jude Medical, St Paul, Minn), which became available in February 2004. The choice of thrombectomy device was at the discretion of the operator. All patients received aspirin 300 mg and unfractionated heparin 5000 to 10 000 IU at the start of the procedure. The use of glycoprotein IIb/IIIa inhibitors and antithrombotic medications was at the discretion of the operator. All patients were advised to maintain lifelong use of aspirin (100 mg/d). Clopidogrel was administered in a loading dose of 300 or 600 mg directly before or immediately after the procedure and was prescribed for at least 1 month in patients treated with bare-metal stents and for at least 6 months in patients treated with drug-eluting stents (75 mg/d). Clinical, angiographic, and procedural characteristics of all PCI-procedures were collected prospectively in an electronic database.

**Study Design**

The study cohort consists of all patients in whom thrombus aspiration was performed in adjunct to the standard primary PCI between August 2001 and October 2007. The retrieved material was fixed in formalin immediately after thrombus aspiration and brought to the department of cardiovascular pathology. After fixation for 24 hours, the material was embedded in paraffin and processed for histology. Serial sections of 5 μm were cut and mounted on glass slides at ≥6 levels and stained with hematoxylin and eosin and elastic von Gieson. A pathologist (A.C.v.d.W.) performed the histopathological analyses while blinded to the angiographic findings, the result of PCI, and the clinical follow-up. The sections were analyzed for the presence or absence of aspirated material. If sufficient material was present (>1 mm³), it was further classified for the presence or absence of thrombus. Thrombus age was classified into 2 groups according to previously published and histopathologically accepted definitions.9,11 Fresh thrombus (<1 day) is composed of layered patterns of fibrin and intact platelets, erythrocytes, and granulocytes (Figure 1A). Older thrombus (>1 day) consists of lytic (1 to 5 days) and/or organized (>5 days) areas. Lytic areas show colliquation necrosis and karyorrhexis of granulocytes (Figure 1B), and organized areas (Figure 1C) are characterized by ingrowth of smooth muscle cells with or without depositions of young connective tissue and ingrowth of capillary vessels. In the present analysis, we distinguished between patients with fresh thrombus only and patients with older thrombus. In some patients, thrombus age could not be classified, mainly because of insufficient material.

**Follow-Up and Outcome**

Information about baseline characteristics (ie, gender, age, risk factors, cardiac history, and medication), procedural characteristics, angiographic characteristics (ie, lesion length, bifurcation, chronic total occlusion, stent implantation, and procedural success), and the use of thrombectomy devices (type of device, device passage, angiographic result, and material obtained) was obtained from the electronic database. Angiographic characteristics such as the presence of distal embolization, preprocedural and postprocedural Thrombolysis in Myocardial Infarction (TIMI) flow, lesion length, and residual stenosis were recorded prospectively by the operator by visual assessment immediately after the procedure. Missing or inconsistent data were completed by review of electronic medical records and hospital case records. Vital status and time of death were obtained from the national population registry (Dutch Central Bureau of Statistics) and verified until November 1, 2007.

**Statistical Analysis**

Data are presented as mean±SD for continuous variables and as frequencies for categorical variables. Differences between patient groups were tested with Student t test or the Mann-Whitney U test or the Mann-Whitney U test.
Results

Figure 2 shows the study flowchart. Thrombus aspiration during primary PCI was performed in 1315 patients. Histopathologically confirmed material was obtained in 989 patients (75%). We identified fresh thrombus in 552 patients (60%) and older thrombus in 372 patients (40%).

Follow-up for mortality from the national population registry was censored at the time of emigration. The follow-up of patients (n = 19) who could not be traced in the national population registry was censored at the date of last contact. Twelve patients without any clinical contact after hospital discharge were excluded from the analyses. To identify independent predictors of mortality at follow-up, variables were tested in a multivariate Cox regression analysis using backward stepwise selection. Variables were removed if P > 0.25.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Table 1. Clinical, Angiographic, and Procedural Characteristics of the 914 Patients With Fresh or Older Thrombus

<table>
<thead>
<tr>
<th></th>
<th>Fresh Thrombus (n=545)</th>
<th>Older Thrombus (n=369)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men, n (%)</td>
<td>409 (75)</td>
<td>264 (72)</td>
<td>0.25</td>
</tr>
<tr>
<td>Age, y</td>
<td>60 (13)</td>
<td>59 (14)</td>
<td>0.70</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>54 (10)</td>
<td>32 (9)</td>
<td>0.57</td>
</tr>
<tr>
<td>Hypercholesterolemia, n (%)</td>
<td>112 (21)</td>
<td>74 (20)</td>
<td>0.87</td>
</tr>
<tr>
<td>Current smoking, n (%)</td>
<td>267 (49)</td>
<td>189 (51)</td>
<td>0.54</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>185 (34)</td>
<td>105 (29)</td>
<td>0.08</td>
</tr>
<tr>
<td>Previous MI, n (%)</td>
<td>39 (7)</td>
<td>37 (10)</td>
<td>0.14</td>
</tr>
<tr>
<td>Previous CABG, n (%)</td>
<td>8 (2)</td>
<td>6 (2)</td>
<td>1.00</td>
</tr>
<tr>
<td>Previous PCI, n (%)</td>
<td>36 (7)</td>
<td>22 (6)</td>
<td>0.78</td>
</tr>
<tr>
<td>Multivessel disease, n (%)</td>
<td>155 (28)</td>
<td>93 (25)</td>
<td>0.29</td>
</tr>
<tr>
<td>Shock, n (%)</td>
<td>60 (11)</td>
<td>48 (13)</td>
<td>0.40</td>
</tr>
<tr>
<td>Total ischemic time, h</td>
<td>3.3±2.4</td>
<td>4.1±4.3</td>
<td>0.001</td>
</tr>
<tr>
<td>Infarct related artery LAD, n (%)</td>
<td>243 (45)</td>
<td>155 (42)</td>
<td>0.46</td>
</tr>
<tr>
<td>Lesion type class C, n (%)†</td>
<td>192 (37)</td>
<td>125 (36)</td>
<td>0.83</td>
</tr>
<tr>
<td>Bifurcation, n (%)†</td>
<td>53 (10)</td>
<td>32 (9)</td>
<td>0.64</td>
</tr>
<tr>
<td>Ostial, n (%)†</td>
<td>34 (6)</td>
<td>30 (8)</td>
<td>0.29</td>
</tr>
<tr>
<td>Calcified, n (%)†</td>
<td>81 (15)</td>
<td>46 (12)</td>
<td>0.33</td>
</tr>
<tr>
<td>Preprocedural TIMI grade 0–1 flow, n (%)†</td>
<td>463 (85)</td>
<td>313 (85)</td>
<td>1.00</td>
</tr>
<tr>
<td>Stent placement, n (%)</td>
<td>513 (94)</td>
<td>339 (92)</td>
<td>0.18</td>
</tr>
<tr>
<td>Lesion length, mm†</td>
<td>16.4±5.4</td>
<td>16.8±5.8</td>
<td>0.73</td>
</tr>
<tr>
<td>Stent length, mm</td>
<td>19.1±4.9</td>
<td>19.4±5.6</td>
<td>0.57</td>
</tr>
<tr>
<td>Stent diameter, mm</td>
<td>3.6±0.5</td>
<td>3.6±0.5</td>
<td>0.19</td>
</tr>
<tr>
<td>Postprocedural TIMI grade 3 flow, n (%)†</td>
<td>494 (92)</td>
<td>323 (89)</td>
<td>0.08</td>
</tr>
<tr>
<td>Residual stenosis ≥20%, n (%)†</td>
<td>16 (3)</td>
<td>15 (4)</td>
<td>0.36</td>
</tr>
<tr>
<td>Distal embolization, n (%)†</td>
<td>66 (12)</td>
<td>68 (18)</td>
<td>0.01</td>
</tr>
<tr>
<td>Peak CK-MB, μg/L‡</td>
<td>343 (278)</td>
<td>338 (283)</td>
<td>0.77</td>
</tr>
</tbody>
</table>

CABG indicates coronary artery bypass grafting; Total ischemic time, time between onset of symptoms and needle time; LAD, left anterior descending artery; and CK-MB, creatine kinase-MB.

†By visual assessment by the operator.

*According to the American College of Cardiology/American Heart Association classification.

Values were available in 349 patients with fresh thrombus and 238 patients with older thrombus.

patients with older thrombus (4.1 versus 3.3 hours; P=0.001), and for the presence of distal embolization. Distal embolization occurred more frequently in patients with older thrombus (18%) than in patients with fresh thrombus (12%). This difference was statistically significant (P=0.01). Virtually all patients received a stent: 92% of the patients with older thrombus and 94% patients with fresh thrombus. The stents placed were predominantly bare metal stents. Postprocedural TIMI grade 3 flow was similar in patients with older thrombus and patients with fresh thrombus (89% versus
92%). Peak creatine kinase-MB values were available in patients not immediately transferred back to the referring hospital (65%). The values were similar in patients with older thrombus and patients with fresh thrombus (343±278 versus 338±283 μg/L).

Figure 3 shows the Kaplan-Meier curves for all-cause mortality in patients with older thrombus, patients with fresh thrombus, and patients with no material or unclassifiable material. In total, 118 of 1303 patients died during follow-up. Cumulative all-cause mortality at 3 years was 11.2% in the patients with older thrombus and 7.4% in the patients with fresh thrombus. Cumulative all-cause mortality at 4 years was 16.0% in the patients with older thrombus and 7.4% in the patients with fresh thrombus (hazard ratio [HR], 1.82; 95% confidence interval [CI], 1.17 to 2.85; P=0.008). In the landmark survival analysis, the mortality rate was significantly higher in patients with older thrombus during the first 14 days (5.7% versus 2.4%; P=0.009). Thereafter, mortality was the same in patients with older thrombus and fresh thrombus (11% versus 5.2%; P=0.20; Figure 4). A difference in the 2-year rate of death was found between patients with older and fresh thrombus both in patients without cardiogenic shock (7.7% versus 5.3%) and in patients in cardiogenic shock (23.3% versus 16.0%) at presentation (Kaplan-Meier curves not shown).

Table 2 shows the results of univariate and multivariate Cox regression analyses for long-term mortality. Univariate analysis identified the presence of older thrombus and a number of clinical and angiographic baseline characteristics as being associated with long-term mortality. Multivariate analysis identified patient age >60 years, a history of coronary artery bypass graft surgery, the presence of cardiogenic shock, diabetes mellitus, female gender, and a postprocedural TIMI grade 0 or 1 flow as independent predictors of...
long-term mortality. The multivariate analysis further identified the presence of older thrombus as an independent predictor for mortality, with an HR of 1.83 (95% confidence interval, 1.14 to 2.93; \(P < 0.01\)). The multivariate HR was identical to the univariate HR, which indicates a separate causal pathway for the relationship between the presence of older thrombus and long-term mortality. The HR for the presence of older thrombus was similar (HR, 1.96; 95% confidence interval, 1.15 to 3.33; \(P < 0.01\)) when the multivariate analysis was restricted to patients with an occluded culprit artery (TIMI grade 0 flow) at the time of presentation.

### Discussion

The present study is the first to relate thrombus age with long-term mortality in STEMI patients undergoing primary PCI. We identified older thrombus in 40% of the patients, which is in line with the 50% prevalence of older thrombus in our previous, smaller thrombectomy study.9 This finding confirms the concept that acute coronary occlusion is often the final stage in a series of nonocclusive atherothrombotic events occurring in the preceding days or weeks. In our analysis, we show that the presence of older thrombus has important prognostic consequences. Our study demonstrates that the presence of older thrombus is an independent predictor of long-term mortality in patients with STEMI treated with thrombus aspiration during primary PCI, in addition to other well-known predictors such as patient age, diabetes mellitus, the presence of shock at hospital admission, and postprocedural TIMI flow. The pathophysiological mechanisms and clinical consequences of this finding require further investigation.

When evaluating the death rates in the landmark survival analysis, we found a significantly higher risk of death during the first 14 days in patients with older thrombus compared with patients with fresh thrombus. After the first 14 days, the death rates were similar in those with older thrombus and those with fresh thrombus. Thus, the difference in mortality occurs primarily within weeks after primary PCI and is sustained over time. Although some differences were seen in baseline characteristics between the patients with older and fresh thrombus, the difference in mortality may not be explained by differences in infarct size, total ischemic time,
or the presence of distal embolization. The decision to perform thrombus aspiration was at the discretion of the operator, who had no knowledge of the presence or absence of older thrombus. Therefore, it is highly unlikely that the difference in mortality between patients with and without older thrombus in the aspirate is due to selection bias. The time to reperfusion has been shown to be a powerful predictor of success in STEMI. The longer total ischemic time in the patients with older thrombus may have diminished the potential benefit of thrombus removal in these patients. However, the observed additional delay of 1 hour cannot reasonably explain the 2-fold difference in survival observed in our study. Furthermore, multivariate analysis showed that total ischemic time was not independently associated with mortality at 4 years and was important only through its association with thrombus age.

The use of a mechanical device for thrombus removal is intuitively attractive for improving reperfusion and survival after primary PCI. Several mechanical devices have been investigated, among them distal or proximal protection devices and thrombus aspiration devices, with various results. Most randomized clinical trials of these mechanical devices did not show a clinical benefit of thrombectomy. The TAPAS trial recently showed that thrombus aspiration with the Export aspiration catheter during primary PCI results in better reperfusion and improved clinical outcomes compared with standard PCI. Multiple explanations exist for why thrombus aspiration resulted in conflicting data on myocardial reperfusion, infarct size, and clinical outcome in these trials. First, the trials evaluated mechanical devices with different designs and operational mechanisms. Some mechanical devices may cause physical damage to the vessel endothelium, which may create new thrombi or distal embolization. Second, the trials had different inclusion and exclusion criteria. In some trials, angiographic evidence of thrombus was required, and thrombus aspiration may be more effective in STEMI patients with a large thrombus burden.

The pathophysiological explanations for our findings remain speculative. The presence of a stabilized older thrombus may causally be related to mortality. It is more likely, however, that it is a biomarker unrelated to causality. The presence of a stabilized older thrombus may be associated with other disease-associated conditions leading to a higher mortality such as more extensive microvascular obstruction, unfavorable remodeling, or more extensive and diffuse coronary disease. A speculative hypothesis may be that patients with older thrombus may have experienced short, temporary, occlusive thrombosis without any clinical event before admission. Repeated episodes of recanalization resulting from partial, spontaneous lysis could be associated with more extensive embolism and microvascular obstruction, resulting in less effective reperfusion compared with patients with fresh thrombus.

Study Limitations

This study has several limitations. First, the risk profile of patients with older thrombus may not be similar to that of patients with fresh thrombus. Unfortunately, we do not have complete information on enzymatic infarct size, although peak creatine kinase-MB values were available in a substan-

tial proportion of patients and showed no difference. Furthermore, we did not prospectively record the presence of preinfarction angina, which may be associated with reduced mortality. However, our previous thrombectomy study showed no relation between thrombus age and the presence of absence of preinfarction angina. Finally, thrombus age cannot be determined noninvasively; therefore, the clinical consequences of our findings remain to be established.

Conclusions

Our study demonstrates that the presence of older thrombus is an independent predictor of long-term mortality in patients with STEMI who are treated with thrombus aspiration during primary PCI. Besides thrombus age, other well-known predictors are older patient age, female gender, diabetes mellitus, presence of shock at hospital admission, and postprocedural TIMI flow. These results show that thrombus composition and thrombus age are associated with clinical outcome after the adjunctive use of mechanical devices during primary PCI. The pathophysiological mechanisms and clinical consequences of this finding require further investigation.

Disclosures

None.

References

Intracoronary thrombus that is 1 to several days or even weeks old is frequently aspirated in patients undergoing primary percutaneous coronary intervention for ST-elevation acute myocardial infarction within 12 hours after symptom onset. This signifies that plaque rupture and subsequent intracoronary thrombus formation on the one hand and coronary occlusion and clinical symptoms on the other hand are often segregated in time. In the present study, the long-term clinical outcome of 1315 patients with acute ST-elevation myocardial infarction after primary percutaneous coronary intervention is correlated with the histopathological findings after thrombus aspiration. The cumulative Kaplan-Meier estimate of all-cause mortality at 4 years was significantly higher in the patients with older thrombus (16.0%) compared with the patients with fresh thrombus (7.4%), with a hazard ratio of 1.82. Multivariate analysis identified the presence of older thrombus as an independent predictor (hazard ratio, 1.83) of long-term mortality, in addition to other established predictors such as patient age, diabetes mellitus, and the presence of shock. At the present time, no methods exist to establish the intracoronary presence of older thrombus noninvasively. Moreover, the pathophysiological mechanism by which older thrombus is related to mortality is unclear. Further studies may elucidate this separate pathway by which older thrombus is related to clinical outcome.
Presence of Older Thrombus Is an Independent Predictor of Long-Term Mortality in Patients With ST-Elevation Myocardial Infarction Treated With Thrombus Aspiration During Primary Percutaneous Coronary Intervention

Miranda C.A. Kramer, Allard C. van der Wal, Karel T. Koch, Johanna P.H.M. Ploegmakers, René J. van der Schaaf, José P.S. Henriques, Jan Baan, Jr, Saskia Z.H. Rittersma, Marije M. Vis, Jan J. Piek, Jan G.P. Tijssen and Robbert J. de Winter

_Circulation._ 2008;118:1810-1816; originally published online October 13, 2008; doi: 10.1161/CIRCULATIONAHA.108.780734

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2008 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/118/18/1810

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/