Coronary Microembolization
From Bedside to Bench and Back to Bedside

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Abstract—Coronary microembolization from the erosion or rupture of a vulnerable atherosclerotic plaque occurs spontaneously in acute coronary syndromes and iatrogenically during percutaneous coronary interventions. Typical consequences of coronary microembolization are microinfarcts with an inflammatory response, contractile dysfunction, and reduced coronary reserve. Apart from transient elevations of creatine kinase and troponin, microemboli can be visualized by intracoronary Doppler and the resulting microinfarcts by late-enhancement nuclear magnetic resonance. Statins, antiplatelet agents, and coronary vasodilators protect against microembolization and microinfarction when started before percutaneous coronary interventions. Distal protection devices can retrieve atherothrombotic debris and prevent its embolization into the microcirculation, but their effect on clinical outcome has been disappointing so far, except for saphenous vein bypass grafts. Devices for aspiration of thrombi and thrombus-derived vasoconstrictor, thrombogenic, and inflammatory substances, however, reduce thrombus burden, improve perfusion, and provide protection in patients with acute myocardial infarction. (Circulation. 2009;120:1822-1836.)

Key Words: coronary disease | imaging | infarction | inflammation | reperfusion | statins | vasoconstriction

The rupture of an atherosclerotic plaque in an epicardial coronary artery does not always result in complete thrombotic coronary occlusion and impending myocardial infarction; milder forms of plaque rupture may leave some residual blood flow and result in the washout of atherothrombotic debris into the coronary microcirculation and its subsequent embolization. Coronary microembolization became a focus of attention about a decade ago with the awareness that coronary microembolization and its sequelae are a frequent iatrogenic complication of percutaneous coronary interventions (PCIs).1,2 However, coronary microembolization was recognized much earlier as being the underlying pathophysiological event in sudden death of patients with unstable angina.3–6 The present review summarizes and updates the pathophysiology of coronary microembolization and the clinical evidence for its diagnosis and its prevention.

The incidence of coronary microembolization is difficult to judge. Spontaneous coronary microembolization occurs, but most likely, only the tip of the iceberg is recognized. Periprocedural coronary microembolization occurs on average in 25% of all PCIs, but its incidence ranges from 0% to 70%, in part depending on the method of its assessment.7 The incidence of periprocedural coronary microembolization depends on factors related to the clinical condition of the patient, notably preexisting kidney disease or underlying unstable angina; factors related to the length8 or complexity of the lesion; and finally, factors related to the procedure, notably the use of a stent rather than percutaneous transluminal coronary angioplasty, the number and duration of inflations, and particularly the use of atherectomy and rotational.7 In patients with an acute myocardial infarction, an angiographic distal filling defect occurred as evidence of coronary microembolization in 7% to 16% of patients and was related to thrombus burden, increased myocardial damage, and reduced effectiveness of reperfusion.9–11 Coronary microembolization occurs also during surgical revascularization but is difficult to distinguish from bypass graft failure.12 Saphenous vein bypass grafts are particularly susceptible to coronary microembolization.7

Pathophysiology of Coronary Microembolization

Morphology
In postmortem analyses of patients who died of sudden death without overt myocardial infarction, microemboli were identified in the microcirculation and characterized by atherosclerotic plaque material, including cholesterol crystals, hyalin, and platelet aggregates; the same material was identified in microemboli that were retrieved from protection devices in patients undergoing PCI.8,13–19 Particle size appeared larger in patients with unstable rather than stable angina20 and with increasing patient age.21 Embolic material retrieved from the particularly microembolization-susceptible saphenous vein...
bypass grafts contains more bioactive atherosclerotic material (necrotic core, foam cells, cholesterol) than that from native vessels (extracellular matrix, smooth muscle cells); also, more debris is retrieved from saphenous vein bypass grafts than from native vessels undergoing PCI. At autopsy, microemboli have been associated with microinfarcts and an inflammatory reaction of the myocardium. Typical microemboli were also identified at autopsy in patients who had died within 3 weeks of balloon angioplasty or thrombolysis.

Microemboli originate from a vulnerable epicardial coronary artery plaque and its erosion or rupture. A necrotic lipid core with a thin fibrous cap predisposes to plaque erosion/rupture and microembolization. It remains unclear why some plaque erosion/rupture with subsequent washout of debris induces microembolization with maintenance of residual blood flow but another plaque erosion/rupture induces myocardial infarction with complete thrombotic coronary occlusion; possibly, the release of vasoconstrictive and thrombogenic factors from the plaque plays a role. In fact, plaque volume is directly related to the amount of coronary vasoconstrictor released. It is also unclear whether the nature of the embolizing plaque material (fibrotic debris with cholesterol versus fresh thrombotic material) has an effect on the consequences of coronary microembolization.

### Experimental Coronary Microembolization

Intracoronary infusion of microspheres in experimental animals induces an immediate but transient decrease of coronary blood flow, followed by a reactive, more prolonged increase in coronary blood flow; this biphasic flow pattern is explained by microvascular occlusion and the subsequent release of adenosine from the microembolized into the surrounding nonembolized myocardium. Both the adenosine-mediated increase in baseline blood flow and the decrease in maximal blood flow secondary to microvascular occlusion contribute to a decrease in coronary reserve in microembolized myocardium. The adenosine-induced hyperemia after coronary microembolization attenuates the decreases in regional contractile function and lactate extraction. Given its normal or slightly elevated baseline coronary blood flow and its contractile dysfunction, microembolized myocardium is characterized by a profound perfusion-contraction mismatch, quite in contrast to myocardium distal to a severe epicardial coronary artery stenosis, in which myocardial blood flow and function are reduced proportionately in a perfusion-contraction matching pattern.

The progressive loss of regional contractile function in microembolized myocardium is not the result of myocardial infarction. In fact, in myocardium with essentially complete loss of contractile function, patchy microinfarcts affect only 2% to 5% of the perfusion territory, and apoptosis is almost negligible. The progressive contractile dysfunction results from an inflammatory reaction to the microinfaracts, characterized by infiltration of leukocytes, including monocytes and macrophages. In line with a causal role for such an inflammatory response, contractile dysfunction recovers spontaneously almost to baseline levels by approximately 1 week after coronary microembolization. More specifically, tumor necrosis factor-α (TNF-α) has been identified as a causal factor for the contractile dysfunction of microembolized myocardium. Increased TNF-α expression is an autocrine/paracrine response of the cardiomyocytes that surround the microinfarcts, possibly triggered by the local shear stress between contracting and noncontracting infarcted myocardium. Exogenous TNF-α causes contractile dysfunction in the absence of coronary microembolization, and conversely, neutralizing antibodies to TNF-α prevent microembolization-induced contractile dysfunction. The signal transduction of TNF-α–mediated contractile dysfunction involves nitric oxide upstream and sphingosine downstream of TNF-α and ultimately an oxidative modification of contractile proteins and reduced calcium responsiveness of the contractile machinery (Figure 1). Thus, reactive oxygen species, inflammatory mediators, and vasoconstrictors contribute to the observed contractile dysfunction. Accordingly, apart from TNF-α–neutralizing antibodies, microembolization-induced contractile dysfunction can be prevented by nonspecific attenuation of inflammation by cortisone or nonspecific attenuation of oxidative stress by vitamin C.

### Interaction With Preconditioning

Ischemic preconditioning is the protection from myocardial infarction afforded by short episodes of myocardial ischemia and reperfusion that precede the sustained myocardial ischemia that ultimately causes infarction. The signal-transduction cascade of the protection conferred by ischemic preconditioning is complex and involves receptor-dependent and -independent triggering molecules, a concerted intracellular protein kinase activation program, and ultimately, prevention of mitochondrial collapse. The laboratory phenomenon of ischemic preconditioning has obvious clinical correlates. The protection obtained through ischemic preconditioning becomes manifest in a “first window” 1 to 2 hours after an ischemic episode and in a more delayed “second window” 24 to 72 hours after an ischemic episode. Transient episodes of angina typically precede acute myocardial infarction, and such transient epi-
sodes of angina involve coronary microembolization and/or myocardial ischemia with reperfusion. Transient episodes of angina may thus either damage the myocardium by microembolization or protect it through ischemic preconditioning.40 In anesthetized open-chest pigs, coronary microembolization failed to raise the interstitial adenosine concentration sufficiently to precondition and protect the myocardium short term, but it increased the infarct size by the additional amount that resulted from prior microembolization.41 However, protection became apparent several hours after coronary microembolization when TNF-α expression was increased, and conversely, protection was abolished by TNF-α-neutralizing antibodies42; therefore, coronary microembolization can elicit a “third window” of preconditioning protection that is triggered by inflammation.43

Animal Models of Coronary Microembolization

The consequences of microembolization in the coronary microcirculation and the dependent myocardium are classically studied with intracoronary injection of microspheres of various diameters44; the use of microspheres with a diameter of ≈40 μm results in microinfarcts of a size and distribution31 that resemble those reported in examples from patients who died of sudden death and had microemboli identified in their coronary microcirculation at autopsy.4 However, microspheres are chemically inert and not chemoattractant and thus are very different from microemboli as identified in patients at autopsy or when retrieved during PCI. In fact, realistic microemboli are composed of platelets, leukocytes, erythrocytes, and atherosclerotic material, including cholesterol crystals (see above); platelet-leukocyte aggregates contribute to impaired microcirculation and ST-segment resolution, creatine kinase release, and left ventricular dysfunction in patients undergoing emergency PCI for acute myocardial infarction.16 Therefore, apart from the physical obstruction, the active thrombogenic, vasoconstrictor, and inflammatory potential of microemboli and their interaction with the vascular wall through selectins, for example, are probably neglected when microspheres are used. Injection of homologous thrombotic material has been used recently to create coronary microembolization in rats, and expression of inflammatory cytokines and left ventricular dysfunction have been reported.45 The combination of traumatic endothelial damage with an external coronary stenosis induces platelet aggregation with subsequent cyclic coronary blood flow variations, microcirculatory vasoconstriction, and microinfarction in dogs.46–48 Intracoronary ADP or intravenous norepinephrine can induce microembolization by platelet aggregates and subsequent microinfarcts in pigs and dogs, respectively.49,50 Apparently, an ideal animal model of coronary microembolization that originates from spontaneous plaque rupture41 and includes both the physical and bioactive properties of microemboli as seen in patients with coronary microembolization does not exist.

Clinical Evidence for Coronary Microembolization

No-Reflow Phenomenon

No or slow reflow after successful PCI is an often-unexpected complication in 0.5% to 1% of patients,52,53 reflects an impairment of microcirculatory blood flow, and carries an adverse prognosis.54,55 Often, coronary microembolization is simplicitically assumed to be the cause of no/slow reflow. Coronary microembolization can certainly contribute to no/slow reflow in the clinical scenario56; however, a profound no-reflow phenomenon is also seen in animal experiments in which a perfectly normal epicardial coronary artery is occluded by an external device that is then released to restore blood flow. The area of no reflow is then confined to the area of infarcted myocardium and is characterized by obstructive capillary damage, ie, it is a consequence and not a cause of infarction.57 Thus, no/slow reflow and coronary microembolization should be viewed as distinct phenomena. Several vasodilator agents, such as nitroprusside, verapamil, and adenosine, have been shown to improve microcirculatory flow with varying degrees of success.58 The recognition that thromboxane A2 and serotonin are released from rupturing plaques59 may provide a potential new treatment option.

Diagnosis of Coronary Microembolization

Biomarkers and Soluble Factors

Apart from frequent but uncharacteristic surface ECG alterations,58 there are characteristic ST-segment shifts in the intracoronary ECG that reflect microinfarction during PCI.59 The microinfarcts that result from spontaneous or iatrogenic, PCI-induced coronary microembolization are reflected by typical transient elevations of creatine kinase and more specifically troponin,7,58,60–63 and troponin elevation is associated with worse prognosis in patients with unstable angina64,65 and PCI.66 The consensus document on the definition of myocardial infarction by the European Society of Cardiology and the American College of Cardiology specifically acknowledges “microemboli from the atherosclerotic lesion that has been disrupted during angioplasty or from the particulate thrombus at the site of the culprit lesion,” and a separate entity of periprocedural myocardial injury is recognized and is related to coronary microembolization.7,67 Whether or not the increased troponin levels that are found in patients with stable angina68 or on routine examination also reflect coronary microembolization is unclear at present.69 Apart from the question of whether increased troponin levels in patients with stable angina reflect coronary microembolization, preprocedural troponin levels in these patients are a stronger predictor of prognosis after PCI than postprocedural troponin levels.70

Reminiscent of the above experimental studies, markers of inflammation are also elevated in clinical scenarios with likely coronary microembolization, such as C-reactive protein and interleukin-6 in patients with complicated acute coronary syndrome.71,72 It is unclear whether such inflammatory biomarkers originate from the rupturing atherosclerotic plaque, the microcirculatory inflammation in response to the
myocardial infarcts, or both. Clearly, the rupturing athero-
sclerotic plaque results not only in the release of vasocon-
strictor and thrombogenic soluble factors that contribute to
impaired microvascular perfusion but also in the release of
TNF-α; these factors can be retrieved by use of a distal
balloon occlusion/aspiration protection device in patients
undergoing PCI. Direct stenting without balloon predila-
tion attenuates troponin release and microvascular dysfunc-
tion. However, more complex interventions with a higher
number, duration, or pressure of balloon inflations and
atherectomy procedures increase the incidence of increases in
periprocedural biomarkers.

Imaging
On intravascular ultrasound examination, a necrotic lipid core
with a thin fibrous cap predisposes to plaque lesion/rupture
and microembolization. The atherosclerotic plaque cavity,
after washout of the debris into the microcirculation, can
be measured and has been shown to be as large as 10 mm³. Reminiscent of the reactive hyperemia seen after experimental
coronary microembolization, patients with potential micro-
embolization after PCI typically have increased baseline coron-
ary blood flow velocity and reduced coronary reserve, which is associated with increased coronary venous adenosine
release and elevated levels of serum creatine kinase and
troponin. More directly, microemboli can be visualized and
counted as high-intensity signals with a Doppler wire, and their
number correlates with troponin release and inversely with
coronary blood flow, coronary reserve, and recovery of myocard-
ial wall function after PCI.

The consequences of PCI-related coronary microemboliza-
tion in the microcirculation and the dependent myocardium
can be visualized by contrast-enhanced nuclear magnetic
resonance imaging (MRI). A fresh late enhancement 24 hours after PCI not related to a potential side-branch occlu-
sion is characteristic and is associated with greater reduction in plaque volume on intravascular ultrasound, reduced
perfusion reserve, and elevated creatine kinase or troponin;
troponin levels correlate with infarct size on MRI. In the
experiment, late-enhancement MRI can be validated
against quantitative staining of infarct size. In pigs with
 coronary microembolization, microinfarcts that exceed 5% of
 the myocardium within the region of interest can be detected
by late-enhancement MRI and late enhancement again
 correlates with troponin (Figure 2). Although intravascular
ultrasound imaging of the underlying vulnerable plaque
and the embolizing particles as high-intensity signals and
MRI imaging of the resulting microinfarcts are already feasible
in patients, new radioactive (including positron emission tomog-
raphy), magnetic, and ultrasonic molecular imaging techniques
are under development for detection of both vulnerable plaques
and microcirculatory consequences.

Prevention/Treatment of
Coronary Microembolization

Statins
Statins not only stabilize a vulnerable atherosclerotic coron-
ary plaque by reducing its lipid content, but their anti-
 inflammatory, pleiotropic action might also attenuate the
inflammatory myocardial responses associated with coronary
microembolization and microinfarction. In support of
this notion, patients given statin therapy when undergoing
PCI have a reduced incidence of periprocedural myocardial
injury, as reflected by creatine kinase and troponin release,
less inflammatory response, and better outcome. It is not clear for how long and at what dose statins must be
given before PCI to protect against coronary microemboliza-
tion. However, even statin loading just before PCI provides
protection; the short-term effects of statin loading cannot be
attributed to plaque stabilization but are a result of the
anti-inflammatory actions of statins or activation of survival
pathways. Apart from any relation to coronary microembolization,
higher doses of statins provide better protection. In addition, high levels of high-density lipoprotein cholesterol
per se protect against PCI-related microinfarction.
**Protection Devices**

The most direct evidence for the clinical importance of coronary microembolization is expected from studies of its prevention by use of protection devices during PCI. Distal protection devices are introduced downstream of the culprit lesion and entail the risk of causing microembolization during their introduction and of occluding side branches; a proximal protection device for occlusion and aspiration remains upstream of the culprit lesion and avoids such risks. The Saphenous vein graft Angioplasty Free of Emboli Randomized Trial (SAFER) has established protection by distal filter devices in patients with stable angina undergoing PCI of saphenous vein aortocoronary bypass grafts, and this together with the FIRE trial (FilterWire EX Randomized Evaluation) has led to a class 1A recommendation in European Society of Cardiology guidelines. However, in

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**Table 1. Statins and PCI**

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Coronary Status, No. of Patients</strong></td>
<td><strong>Target Vessel, No. of Treated Culprit Lesions</strong></td>
</tr>
<tr>
<td>Acute Coronary Syndrome</td>
<td>Not Attributable to NSTEMI or STEMIs</td>
</tr>
<tr>
<td>Stable</td>
<td>NSTEMI</td>
</tr>
<tr>
<td>296</td>
<td>229 vs 67</td>
</tr>
<tr>
<td>5052</td>
<td>1337 vs 3715</td>
</tr>
<tr>
<td>425</td>
<td>275 vs 150</td>
</tr>
<tr>
<td>451</td>
<td>226 vs 225</td>
</tr>
<tr>
<td>400</td>
<td>218 vs 182</td>
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<tr>
<td>552</td>
<td>273 vs 279</td>
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<tr>
<td>803</td>
<td>174 vs 629</td>
</tr>
<tr>
<td>119</td>
<td>102 vs 98</td>
</tr>
<tr>
<td>200</td>
<td>40 vs 346</td>
</tr>
<tr>
<td>386</td>
<td>46 vs 41</td>
</tr>
<tr>
<td>253</td>
<td>86 vs 167</td>
</tr>
<tr>
<td>950</td>
<td>327 vs 623</td>
</tr>
<tr>
<td>1552</td>
<td>615 vs 937</td>
</tr>
<tr>
<td>3702</td>
<td>2052 vs 1650</td>
</tr>
<tr>
<td>153</td>
<td>76 vs 77</td>
</tr>
<tr>
<td>76</td>
<td>38 vs 38</td>
</tr>
<tr>
<td>171</td>
<td>86 vs 85</td>
</tr>
<tr>
<td>Statins just before PCI, yes vs no</td>
<td>445</td>
</tr>
<tr>
<td>383</td>
<td>228 vs 222</td>
</tr>
<tr>
<td>Statins just after PCI, yes vs no</td>
<td>1677</td>
</tr>
<tr>
<td>Statins vs statins before PCI</td>
<td>4162</td>
</tr>
<tr>
<td>4162</td>
<td>2099 vs 2063</td>
</tr>
<tr>
<td>5407</td>
<td>2688 vs 2719†</td>
</tr>
<tr>
<td>40</td>
<td>15 vs 15‡</td>
</tr>
</tbody>
</table>

NSTEMI indicates non-ST-elevation myocardial infarction; STEMIs, ST-elevation myocardial infarction; SVGs, saphenous vein graft; MACE, major adverse cardiac events; R, randomized study; CRP, C-reactive protein; ↓, decreased damage; ↑, increased damage; †, no change; ARMYDA, Atorvastatin for Reduction of Myocardial Damage During Angioplasty; ARMYDA-RECAPTURE, Atorvastatin for Reduction of Myocardial Damage During Angioplasty; LIPS, Lescol Intervention Prevention Study; PROVE IT-TIMI 22, Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction 22; TNT, Treating to New Targets; and STRAP, Statins for Regeneration After Acute Myocardial Infarction and PCI.

*Eighty milligrams of atorvastatin vs 40 mg of pravastatin.
†Eighty milligrams vs 10 mg of atorvastatin.
‡Eighty milligrams of vs 20 mg of atorvastatin.
the aggregate, the existing data on distal protection devices, all of which apart from the SAFER trial were derived from patients with acute myocardial infarction, are disappointing (Table 2), and this view is supported by meta-analyses and editorial comments.\(^{129,150–152}\) No protection is seen with the use of filter devices during PCI of native coronary vessels, and many studies revealed no protection, whether with biomarkers, imaging, or major cardiac events as end points, with the use of balloon occlusion/aspiration devices in either native or saphenous vein bypass vessels. In addition, no difference between the use of filter or distal balloon occlusion/aspiration devices in saphenous vein bypass grafts is apparent, which would be expected if small particles and/or soluble factors that are not trapped by filter devices were of major importance. Given the evidence that protection against coronary microembolization (for example, by statins) is beneficial, a satisfying explanation for the apparent lack of protection afforded by distal devices is not available; possibly, there is damage by the additional instrumentation and/or side-branch occlusion that offsets any protection.

**Table 2. Protection Devices for Use in PCI**

<table>
<thead>
<tr>
<th>Coronary Status, No. of Patients</th>
<th>Target Vessel, No. of Treated Culprit Lesions</th>
<th>Surrogate Parameter</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable NSTEMI or STEMI</td>
<td>Native, Yes vs No</td>
<td>Biomarker Imaging Clinical End Point: MACE Reference</td>
<td></td>
</tr>
<tr>
<td>Not Attributable to NSTEMI or STEMI</td>
<td>STEMI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Filter device vs conventional PCI</td>
<td>106 53 vs 53</td>
<td>↓ ↓</td>
<td>Limbruno et al(^{18})</td>
</tr>
<tr>
<td></td>
<td>200 100 vs 100</td>
<td></td>
<td>PROMISE(^{135}) (R)</td>
</tr>
<tr>
<td></td>
<td>140 70 vs 70</td>
<td></td>
<td>PREMIAR(^{136}) (R)</td>
</tr>
<tr>
<td></td>
<td>100 51 vs 49</td>
<td></td>
<td>UPFLOW(^{136}) (R)</td>
</tr>
<tr>
<td></td>
<td>626 312 vs 314</td>
<td></td>
<td>DEDICATION(^{138}) (R)</td>
</tr>
<tr>
<td>Distal balloon occlusion vs conventional PCI</td>
<td>801 442 vs 433</td>
<td>↓ ↓ ↓</td>
<td>SAFER(^{130}) (R)</td>
</tr>
<tr>
<td></td>
<td>501 277 vs 249</td>
<td></td>
<td>PROMISE(^{135}) (R)</td>
</tr>
<tr>
<td></td>
<td>191 81 vs 110</td>
<td></td>
<td>PREMIAR(^{136}) (R)</td>
</tr>
<tr>
<td></td>
<td>58 30 vs 28</td>
<td></td>
<td>UPFLOW(^{136}) (R)</td>
</tr>
<tr>
<td></td>
<td>151 79 vs 72</td>
<td></td>
<td>DEDICATION(^{138}) (R)</td>
</tr>
<tr>
<td></td>
<td>341 173 vs 168</td>
<td></td>
<td>ASPARAGUS(^{143}) (R)</td>
</tr>
<tr>
<td></td>
<td>120 57 vs 63*</td>
<td></td>
<td>Ochala et al(^{144}) (R)</td>
</tr>
<tr>
<td></td>
<td>39 19 vs 20</td>
<td></td>
<td>Hahn et al(^{145}) (R)</td>
</tr>
<tr>
<td></td>
<td>161 60 vs 56</td>
<td></td>
<td>Tahk et al(^{146}) (R)</td>
</tr>
<tr>
<td>Filter device vs distal balloon occlusion</td>
<td>651 348 vs 334</td>
<td>☐ ☐ ☐</td>
<td>FIRE(^{131}) (R)</td>
</tr>
<tr>
<td></td>
<td>572 296 vs 276</td>
<td>☐, ↓†</td>
<td>FIRE(^{132}) (R)</td>
</tr>
<tr>
<td></td>
<td>624 317 vs 307</td>
<td>☐</td>
<td>FIRE(^{133}) (R)</td>
</tr>
<tr>
<td></td>
<td>631 318 vs 313</td>
<td>☐ ☐ ☐</td>
<td>PRIDE(^{147}) (R)</td>
</tr>
<tr>
<td></td>
<td>797 541 vs 272‡</td>
<td>☐</td>
<td>AMEthyst(^{148}) (R)</td>
</tr>
<tr>
<td>Proximal vs distal protection device</td>
<td>594 315 vs 329§</td>
<td>☐</td>
<td>PROXIMAL(^{149}) (R)</td>
</tr>
</tbody>
</table>

NSTEMI indicates non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction; SVG, saphenous vein graft; MACE, major adverse cardiac events; R, randomized study; ↓, decreased damage; ☐, no change; PROMISE, Protection Devices in PCI Treatment of Myocardial Infarction for Salvage of Endangered Myocardium; PREMIAR, Protection of Distal Embolization in High-Risk Patients with Acute ST-Segment Elevation Myocardial Infarction; UPFLOW, Use of Protective FilterWire to Improve Flow in Acute Myocardial Infarction; DEDICATION, Drug Elution and Distal Protection in ST-Elevation Myocardial Infarction; SAFER, Saphenous Vein Graft Angioplasty Free of Embolized Randomized Trial; EMERALD, Enhanced Myocardial Efficacy and Recovery by Aspiration of Liberated Debris; MICADO, Multicenter Investigation of Coronary Artery Protection With a Distal Occlusion Device in Acute Myocardial Infarction; ASPARAGUS, Aspiration of Liberated Debris in Acute Myocardial Infarction With GuardWire Plus; FIRE, FilterWire EX Randomized Evaluation; PRIDE, Protection During Saphenous Vein Graft Intervention to Prevent Distal Embolization; AMEthyst, Assessment of the Medtronic AVE Interceptor Saphenous Vein Graft Filter System; and PROXIMAL, Proximal Protection During Saphenous Vein Graft Intervention.

*Conventional PCI with abciximab.
†in small vessels <3.03 mm.
‡Comparison of Interceptor PLUS vs GuardWire and FilterWire.
§70 Lesions without any protection.
In the setting of acute myocardial infarction, the removal of thrombotic material and of thrombus-related soluble substances reduces thrombus burden, improves myocardial perfusion, and provides protection, again supporting the pathophysiological importance of coronary microembolization. Thromboaspiration before conventional PCI is primarily practiced with angiographically visible thrombi but is clearly also protective without prior visualization of thrombi (Table 3). Thromboaspiration protects when performed manually or with the use of automated devices, which are more effective but also larger. It is not clear why thromboaspiration offers protection but distal protection fails to protect even when both strategies are used in patients with acute myocardial infarction and with the same end points (Tables 2 and 3). Prevention of formation of microemboli by thromboaspiration rather than their retrieval by distal protection devices once they are formed, as well as the iatrogenic induction of microembolization by advancement of the protection device distal to the culprit lesion, are potential explanations; in addition, a filter pore size of 80 to 100 μm may still permit the embolization of smaller particles, which are nevertheless of considerable impact in animal studies (see above).

### Table 3. Thromboaspiration in Acute Myocardial Infarction

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>Acute Coronary Syndrome</td>
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<tr>
<td>Stable NSTEMI or STEMI</td>
<td></td>
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<tr>
<td>Not Attributable to NSTEMI or STEMI</td>
<td>Not Attributable to Native or SVG, Yes vs No</td>
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<td>SVG, Yes vs No</td>
<td>Biomarker Imaging Clinical End Point: MACE Reference</td>
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<td>Target Vessel, No. of Treated Culprit Lesions</td>
<td>Surrogate Parameter</td>
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<tr>
<td>Thromboaspiration vs conventional PCI</td>
<td></td>
</tr>
<tr>
<td>797</td>
<td>400 vs 397</td>
</tr>
<tr>
<td>61</td>
<td>30 vs 31</td>
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<tr>
<td>92</td>
<td>46 vs 46</td>
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<td>100</td>
<td>50 vs 50</td>
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<td>72</td>
<td>40 vs 32</td>
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<td>201</td>
<td>100 vs 101</td>
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<td>76</td>
<td>38 vs 38</td>
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<tr>
<td>148</td>
<td>74 vs 74</td>
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<td>480</td>
<td>240 vs 240</td>
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<td>160</td>
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<td>175</td>
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<td>Thromboaspiration device vs thromboaspiration device</td>
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<tr>
<td>160</td>
<td>80 vs 80*</td>
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</tbody>
</table>

NSTEMI indicates non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction; SVG, saphenous vein graft; MACE, major adverse cardiac events; R, randomized study; ↓, decreased damage; ↑, increased damage; ☒, no change; X-TRACT, X-sizer for Treatment of Thrombus and Atherosclerosis in Coronary Applications; X AMINE ST, X-sizer in AMI for negligible embolization and optimal ST resolution; DEAR-MI, Dethrombosis to Enhance Acute Reperfusion in Myocardial Infarction; AIMI, AngioJet in Acute Myocardial Infarction; REMEDIA, Randomized Evaluation of the Effect of Mechanical Reduction of Distal Embolization by Thrombus-Aspiration in Primary and Rescue Angioplasty; MCE-REMEDIA, Myocardial Contrast Echocardiography sub-study of the REMEDIA trial; TAPAS, Thrombus Aspiration During Percutaneous Coronary Intervention in Acute Myocardial Infarction Study; RETAMI, Randomized Evaluation of Thrombus Aspiration by two thrombectomy devices in acute Myocardial Infarction; and EXPIRA, Thrombectomy With Export Catheter in Infarct-Related Artery During Primary Percutaneous Coronary Intervention.

*Comparison of Export-Medtronic vs Diver-Invatec protection device.

In the setting of acute myocardial infarction, the removal of thrombotic material and of thrombus-related soluble substances reduces thrombus burden, improves myocardial perfusion, and provides protection, again supporting the pathophysiological importance of coronary microembolization. Thromboaspiration before conventional PCI is primarily practiced with angiographically visible thrombi but is clearly also protective without prior visualization of thrombi (Table 3). Thromboaspiration protects when performed manually or with the use of automated devices, which are more effective but also larger. It is not clear why thromboaspiration offers protection but distal protection fails to protect even when both strategies are used in patients with acute myocardial infarction and with the same end points (Tables 2 and 3). Prevention of formation of microemboli by thromboaspiration rather than their retrieval by distal protection devices once they are formed, as well as the iatrogenic induction of microembolization by advancement of the protection device distal to the culprit lesion, are potential explanations; in addition, a filter pore size of 80 to 100 μm may still permit the embolization of smaller particles, which are nevertheless of considerable impact in animal studies (see above).

### Antiplatelet Agents and Coronary Vasodilators

Of the many studies on the use of antiplatelet and vasodilator agents in PCI, we considered only those in which the respective agent had objective signs of myocardial damage...
(biomarker, imaging) as an end point, because only with reduction of myocardial damage can the targeted thrombotic and/or vasoconstrictor mechanism be regarded as a cause rather than a consequence of myocardial infarction (see above on the slow-reflow/no-reflow phenomenon). Clearly, there are a number of studies in which the use of antiplatelet agents in patients with stable angina or acute coronary syndromes and vasodilator agents in patients with acute coronary syndromes attenuated myocardial damage or reduced adverse events (Table 4).174–186 which supports the contribution of thrombotic and vasoconstrictor mechanisms to the pathophysiology of coronary microembolization; however, it is unclear whether the respective agent actually prevented the formation of microemboli (possible with antiplatelet agents) or attenuated their consequences in the microcirculation (possible with coronary vasodilators).

In conclusion, coronary microembolization occurs spontaneously and possibly much more frequently than is recognized; it is also a frequent complication during PCI. The consequences of coronary microembolization are reduced coronary reserve, microinfarcts with inflammatory responses, and myocardial dysfunction (Figure 3). Statins, antiplatelet agents, and coronary vasodilators protect against coronary microembolization and its consequences. The use of distal protection devices has thus far been disappointing; however, in recent studies, thromboaspiration reduced thrombus burden and conferred protection in patients with acute myocardial infarction.

**Practical Recommendations and Perspectives**

Coronary microembolization has prognostic relevance for the patient. The incidence of spontaneous minor plaque rupture with coronary microembolization is not known definitively. For comparison, however, silent cerebral infarction secondary to microembolization occurs in 17% of asymptomatic patients with carotid artery stenosis.187 Increased levels of creatine kinase or troponin, respectively, which are characteristic consequences of microembolization-induced myocardial microinfarcts, are associated with worse prognosis in patients with coronary microembolization.
patients with coronary artery disease. Periprocedural coronary microembolization is associated with worse prognosis in some studies, as detailed in Table 2. A necrotic lipid core with a thin fibrous cap seen during intravascular ultrasound imaging predisposes to plaque erosion/rupture with coronary microembolization and thus identifies patients at risk, but at the same time, the imaging procedure per se entails the risk of inducing coronary microembolization. In the absence of firm evidence from randomized clinical trials, we recommend the use of occlusion/aspiration devices during PCI of saphenous vein bypass grafts, because they retrieve all debris material, including smaller particles that would otherwise pass through a filter pore and all soluble vasoconstrictor, thrombogenic, and inflammatory factors. We realize that protection devices have not consistently shown benefits in native vessels (Table 2), but in line with a recent meta-analysis on the use of protection devices in primary/rescue PCI, we are convinced of the pathophysiological concept and recommend the use of filter devices in native vessels with complex stenoses and complex procedures, when the diameter of the vessel permits use of a protection device. We recommend the use of a proximal rather than a distal protection device in vessels with significant side branches that might otherwise experience shunting of microemboli into them. In patients with acute myocardial infarction, we recommend the use of a thromboaspiration device when thrombi are angiographically visible.

Ongoing research is directed toward 1) improvements in imaging agents and modalities to detect plaque rupture and the consequent microcirculatory disturbances, as well as to 2) improvements in device technology to retrieve atherothrombotic material and prevent it from microembolization (eg, PREPARE [Proximal Embolic Protection in Acute MI and Resolution of ST Elevation], RETRIEVE [Use of the Fiber-Net Embolic Protection System in Saphenous Vein Grafts], and VAMPIRE [Vacuum Aspiration Thrombus Removal]) including the long-term success of such devices (eg, ATTEMPT [Long-Term Clinical Efficacy of Thrombectomy Devices in Acute ST Elevation Myocardial Infarction]) and 3) improvements in stent technology to prevent the release of microemboli from the culprit plaque. Pharmacological research is directed toward better plaque stabilization (eg, attenuation of pathological metalloproteinase activity) and more efficient prevention of platelet aggregation (eg, CIPAMI [Clopidogrel Administered Prehospital to Improve Primary PCI in Patients With Acute Myocardial Infarction]), platelet leukocyte interaction, and microcirculatory vasoconstriction. Pharmacological research is directed toward better plaque stabilization (eg, attenuation of pathological metalloproteinase activity) and more efficient prevention of platelet aggregation (eg, CIPAMI), platelet-leukocyte interaction, and microcirculatory vasoconstriction.

Disclosures

None.

References

9. Henriques JP, Zijlstra F, Ottewanger JP, de Boer MJ, van’t Hof AWJ, Hoontje JCA, Suryapranata H. Incidence and clinical significance of...


100. Bell RM, Yellon DM. Atorvastatin, administered at the onset of reperfusion, and induction of lipid lowering protects the myocardium by up-regulating a pro-survival pathway. J Am Coll Cardiol. 2003;41:508–515.


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