No reflow in ACS: Treatment strategies and Developments

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No-reflow is defined as a failure to restore antegrade normal coronary flow despite appropriate treatment of coronary obstruction.

The prevalence of this complication occurs in 0.6% to 5% of PCIs.

The incidence of no-reflow appears to be highest in patients undergoing PCI of SVGs, during acute myocardial infarction (AMI) or during rotational atherectomy.

It can occur in as high as 50% of PCI cases involving the treatment of thrombus-containing lesions.

A history of diabetes mellitus, or the absence of preinfarct angina, was found to increase the risk of no-reflow.
Mechanisms responsible for No-Reflow

- Mechanical obstruction for distal embolization of thrombus and/or atherosclerotic debris.
- Extrinsic coagulation pathway. Endothelial cell dysfunction/vasoconstriction induces exposure of TF leading to thrombosis.
Platelet aggregation

Distal embolization

Spasm of microcirculation

Neutrophilic plugging

Tissue edema

increased oxidative stress

--a combination of these factors

Distal embolization

- Emboli originate from thrombus and atherosclerotic plaques
- A small number of emboli is unlikely to affect coronary blood flow
- Emboli (>200 μm diameter) can obstruct pre-arterioles, causing infarctlets
- Doppler guidewire in patients undergoing PPCI allows detection of high-intensity transient signals and counting of embolic particles
- Average number of emboli throughout PPCI is 12
  - However, none detected in patients with distal protection device

![Graph showing comparison between Non-DP group and DP group](image-url)
Independent predictors of distal embolization: thrombus

- Angiographic thrombus with greatest linear dimension >3 times reference lumen diameter
- Cutoff pattern – No taper before occlusion
- Accumulated thrombus proximal to lesion
- Floating thrombus
- Persistent contrast medium distal to the obstruction
- Reference lumen diameter >4 mm
Risk Factors of No-Reflow

- Thrombus-containing lesions
- Degenerative SVG grafts
- PCI for AMI
- Rotablator atherectomy
- Lipid pool-like images on intravascular ultrasound
- High-risk clinical status

Clinical Risk Factors of No-Reflow

- AMI PPCI
- Angina after MI
- Unstable angina
- Cardiac shock
- Hyperglycemia
- Hyper- TC, TG, LDL
- Hyper - NT-pro BNP
Predictors of no-reflow

- Killip class
- Number of Q waves
- Wall motion score on UCG
- Initial CAG show TIMI 0 grade flow

- Preinfarction angina: attenuate no-reflow, due to ischemia preconditioning
TIMI frame count

- TIMI frame count is defined as the number of cineframes required for contrast to reach a standardized distal coronary landmark in the culprit vessel.
- The number is expressed based upon a cinefilming rate of 30 frames/second.
TIMI myocardial perfusion (TMP) grades

- **TMP grade 3**: Normal ground glass appearance of blush. Dye mildly persistent at end of washout.
- **TMP grade 2**: Dye strongly persistent at end of washout. Gone by next injection.
- **TMP grade 1**: Stain present. Blush persists on next injection.
- **TMP grade 0**: No or minimal blush.

Mortality (%)

- TMP grade 3: p = 0.05
- TMP grade 2: 4.4%
- TMP grade 1: 5.1%
- TMP grade 0: 6.2%

n = 203
n = 46
n = 79
n = 434

MARK A APPLEBY et al. Heart 2001;86:485-486
TIMI myocardial perfusion grade (TMPG) (or myocardial blush grade)

- A novel technique to assess myocardial perfusion or “blush” on a coronary angiogram.
- TMP grade correlates with the final infarct size in patients with AMI treated with thrombolysis.
- Also a reliable indicator of the degree of myocardial salvage achieved with reperfusion therapy.

Dibra et al. JACC Vol. 41, No. 6, 2003:925–9
Prevention

- The use of thrombectomy
- Distal embolic protection
- Direct stenting
- Systemic infusion of glycoprotein IIb/IIIa (GP IIb/IIIa) inhibitors
- Intracoronary infusion of vasodilating or antithrombotic/thrombolytic agents
Mechanical Strategies to Prevent Reperfusion No-Reflow

Clot extraction

Stent

Filter

Thrombectomy

- For patients undergoing primary PCI, we suggest not performing routine manual thrombectomy (thrombus aspiration; aspiration thrombectomy).
- While thrombus burden can be reduced by using manual thrombectomy, the evidence does not demonstrate a significant benefit from its routine use.
- With regard to mechanical (rheolytic) thrombectomy, the results of randomized trials do not show benefit in the aggregate.
### TOTAL, TASTE & TAPAS trials

<table>
<thead>
<tr>
<th></th>
<th>Pt. of manual thrombectomy followed by PCI or PCI alone</th>
<th>Primary outcome</th>
<th>results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TOTAL</strong></td>
<td>N=10732</td>
<td>cardiovascular death, recurrent MI, cardiogenic shock, NYHA IV heart failure</td>
<td>347 vs. 351 events, hazard ratio 0.9, 95% CI 0.85-1.15</td>
</tr>
<tr>
<td><strong>TASTE</strong></td>
<td>N=7244</td>
<td>death from any cause at 30 days; mortality at 1 year</td>
<td>No difference between two groups</td>
</tr>
<tr>
<td><strong>TAPAS</strong></td>
<td>N=1071</td>
<td>myocardial blush grade of 0 or 1 (absent or minimal myocardial reperfusion)</td>
<td>17.1%: 26.3% (p&lt;0.001)</td>
</tr>
</tbody>
</table>

- Key safety outcome of stroke occurred more often with thrombectomy
- Risks of all-cause mortality (the primary end point) and MACE, a composite of death, MI, and target vessel revascularization, were lower with aspiration thrombectomy

TOTAL trial: no differences between groups in primary endpoint

<table>
<thead>
<tr>
<th>Table 1. Clinical Outcomes at 180 Days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Thrombectomy + PCI</strong></td>
</tr>
<tr>
<td><strong>PCI Alone</strong></td>
</tr>
<tr>
<td><strong>HR (95% CI)</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Primary Outcome + Stent Thrombosis or TVR</strong></td>
</tr>
<tr>
<td><strong>Cardiovascular Death</strong></td>
</tr>
<tr>
<td><strong>Recurrent MI</strong></td>
</tr>
<tr>
<td><strong>Cardiogenic Shock</strong></td>
</tr>
<tr>
<td><strong>NYHA Class IV Heart Failure</strong></td>
</tr>
<tr>
<td><strong>Stent Thrombosis</strong></td>
</tr>
<tr>
<td><strong>TVR</strong></td>
</tr>
<tr>
<td><strong>Major Bleeding</strong></td>
</tr>
</tbody>
</table>

Distal embolic protection devices

- Increasingly used with PCI in SVGs due to the substantial potential for embolization of both thrombus and atheromatous material.
- A lack of benefit in trials; do not recommend as routine adjunctive therapy to primary PCI with STEMI patients.
- EMERALD PROMISE DEDICATION trials.

No-reflow was most common in patients with a ruptured plaque treated without distal protection.

Clinical benefit from distal protection (as estimated from ST segment resolution, myocardial blush grade, and left ventricular ejection fraction) was only seen in patients with ruptured plaque.

Macrophage with platelets and fibrin (A), lipid-containing macrophage (B), and lipid drops (C)

Direct stenting and deferred stenting

- Direct stenting, without predilation, may lower the incidence of no-reflow.
- In high-risk STEMI patients, deferred stenting in primary PCI reduced no-reflow and increased myocardial salvage.

**Table 2**

<table>
<thead>
<tr>
<th>Primary and Secondary Angiographic and Electrocardiographic Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immediate Stenting</strong> (n = 49)</td>
</tr>
<tr>
<td><strong>Primary outcome:</strong></td>
</tr>
<tr>
<td>Ne-o-no-reflow (TIMI 0-1)</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>Secondary angiographic outcome</td>
</tr>
<tr>
<td>No-reflow (TIMI grade 0 or 1)</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>Ne-o-no-reflow (TIMI grade 3)</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>Risk TIMI coronary flow grade post-PCI</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>0/1</td>
</tr>
<tr>
<td>Risk TIMI myocardial blush grade post-PCI</td>
</tr>
<tr>
<td>Missing</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>0/1</td>
</tr>
</tbody>
</table>

Systemic GP IIb/IIIa inhibitors

- It is unclear whether GP IIb/IIIa inhibitors when infused peripherally reduce the incidence of no-reflow
- Do not recommend the routine use of glycoprotein (GP) IIb/IIIa inhibitors
- Randomized trial/ CADILLAC trials

Intracoronary administration of tirofiban for no-reflow phenomenon

Figure 2 Forest plot of OR for TIMI flow transformation.

Figure 3 Forest plot of OR for MACE.
Effect of abciximab on clinical outcome

Figure 1. Cumulative combined frequency of death, reinfarction and TLR during 30-day follow-up in the two treatment groups.

Figure 2. Event-free survival curves for death, reinfarction and TLR in the two treatment groups.

Figure 3. Cumulative distribution curves for acute gain and late loss for the two treatment groups.

Intracoronary infusions:
Vasodilator therapies- adenosine & verapamil

- Adenosine and verapamil are of uncertain benefit when given for slow coronary flow in STEMI.
- However, we use these agents from time to time despite convincing evidence of benefit.
- Either agent reduced short-term, all-cause mortality or non-fatal myocardial infarction; In addition, there was an increase in the risk of adverse effects such as bradycardia or hypotension with adenosine.
Adenosine improves post-procedural coronary flow

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>adenosine Events</th>
<th>Total</th>
<th>placebo Events</th>
<th>Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMISTAD I</td>
<td>10</td>
<td>119</td>
<td>6</td>
<td>117</td>
<td>3.7%</td>
<td>1.70 [0.60, 4.83]</td>
<td></td>
</tr>
<tr>
<td>AMISTAD II</td>
<td>146</td>
<td>1414</td>
<td>83</td>
<td>703</td>
<td>65.7%</td>
<td>0.86 [0.65, 1.14]</td>
<td></td>
</tr>
<tr>
<td>ATTACC</td>
<td>32</td>
<td>302</td>
<td>39</td>
<td>306</td>
<td>22.9%</td>
<td>0.61 [0.49, 1.33]</td>
<td></td>
</tr>
<tr>
<td>Desmet</td>
<td>2</td>
<td>56</td>
<td>2</td>
<td>54</td>
<td>1.3%</td>
<td>0.96 [0.13, 7.09]</td>
<td></td>
</tr>
<tr>
<td>Fokkema</td>
<td>3</td>
<td>226</td>
<td>2</td>
<td>222</td>
<td>1.3%</td>
<td>1.48 [0.24, 8.94]</td>
<td></td>
</tr>
<tr>
<td>Grycier</td>
<td>0</td>
<td>35</td>
<td>0</td>
<td>35</td>
<td></td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>Marzilli</td>
<td>0</td>
<td>27</td>
<td>5</td>
<td>27</td>
<td>3.6%</td>
<td>0.07 [0.00, 1.42]</td>
<td></td>
</tr>
<tr>
<td>Stoel</td>
<td>3</td>
<td>27</td>
<td>1</td>
<td>22</td>
<td>0.6%</td>
<td>2.63 [0.25, 27.19]</td>
<td></td>
</tr>
<tr>
<td>Vijayalakshmi</td>
<td>0</td>
<td>51</td>
<td>1</td>
<td>50</td>
<td>1.0%</td>
<td>0.32 [0.01, 8.05]</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI) 2257 1536 100.0% 0.87 [0.69, 1.09]

Total events 196 139

Heterogeneity: Chi² = 5.90, df = 7 (P = 0.55); I² = 0%
Test for overall effect: Z = 1.20 (P = 0.23)

Favours Adenosine  Favours Placebo
Adenosine improves post-procedural coronary flow

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
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<th>placebo</th>
<th>Total</th>
<th>Weight</th>
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<tr>
<td>AMISTAD I</td>
<td>0</td>
<td>6</td>
<td>117</td>
<td>41.4%</td>
<td>0.07 [0.00, 1.29]</td>
</tr>
<tr>
<td>Fokkema</td>
<td>2</td>
<td>1</td>
<td>222</td>
<td>6.3%</td>
<td>1.97 [0.18, 21.92]</td>
</tr>
<tr>
<td>Marzilli</td>
<td>1</td>
<td>7</td>
<td>27</td>
<td>42.7%</td>
<td>0.17 [0.01, 0.97]</td>
</tr>
<tr>
<td>Tian</td>
<td>1</td>
<td>0</td>
<td>12</td>
<td>9.5%</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Vijayalakshmi</td>
<td>0</td>
<td>1</td>
<td>51</td>
<td>9.5%</td>
<td>0.32 [0.01, 8.05]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>435</td>
<td>430</td>
<td>100.0%</td>
<td></td>
<td>0.23 [0.08, 0.70]</td>
</tr>
<tr>
<td>Total events</td>
<td>3</td>
<td>15</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 4.16, df = 3 (P = 0.24); I^2 = 28\%$

Test for overall effect: $Z = 2.59 (P = 0.010)$
**Intracoronary nitroprusside**

- Doses of 50 to 200 µg, has shown promising results when given alone or with intracoronary adenosine.

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![Graph showing cumulative incidence of MACEs over follow-up days between Group A and Group B.](image-url)

*J Am Coll Cardiol 2001; 37:1335
Intracoronary infusions: Antithrombotic/thrombolytic therapies

- Intracoronary abciximab and low dose intracoronary streptokinase (250,000 U) have the ability to improve microvascular perfusion.

JACC Cardiovasc Interv 2010; 3:928
Chronic statin therapy

- An observational study from Japan of 293 consecutive patients.
- Statin-treated patients had a much lower rate of no-reflow (9 versus 35 percent), better wall motion, and a higher left ventricular ejection fraction.
- Statin therapy reduces myocardial injury, stabilizes plaque after PCI.
Support treatment

- For those patients with hypotension and/or hypoperfusion, intravenous vasopressors, inotropic agents, and IABP support may be of benefit.
No-reflow usually presents with acute ischemia, EKG changes, chest pain, atrioventricular block, and hypotension.

The occurrence of no-reflow has been associated with adverse short- and long-term outcomes.

Prognosis

- p for trend <0.0001 for all three outcomes.

Prognosis

- No-reflow has been associated with an increase in acute MI of up to 32% and a 15% higher incidence of death.

- The long-term detrimental effect of no-reflow has been documented to include increased risk for cardiac death, congestive heart failure, malignant arrhythmias and decrease in ejection fraction.
Prognosis of No-reflow during PCI in 1 and 5 years

**Figure 4.** Probability of 1-year survival among patients with normal flow and no reflow after primary PCI. HR indicates hazard ratio.

**Figure 2.** Kaplan-Meier Curves of 5-Year Mortality

Red line = reflow group; blue line = no-reflow group. CI = confidence interval; HR = hazard ratio.
SUMMARY and RECOMMENDATIONS

- PCI in STEMI patients establishes normal or near normal antegrade blood flow, as assessed by the Thrombolysis in Myocardial Infarction (TIMI) flow grade 3, in over 90 percent of cases.

- The most common causes of TIMI flow grade ≤2 are persistent stenosis, thrombus, dissection, spasm, or distal macroembolism.

- Age ≥70 years, diabetes, longer time to reperfusion, initial TIMI flow grade ≤1, left ventricular ejection fraction <50 percent, heart failure on presentation, and incomplete ST segment elevation resolution are predictors of suboptimal reperfusion.
SUMMARY and RECOMMENDATIONS

- Direct stenting lessens the likelihood of no-reflow.
- The benefit of glycoprotein (GP) IIb/IIIa inhibitors or the intracoronary infusion of adenosine remains speculative.
- We suggest not routinely performing thrombus aspiration in primary PCI. It is reasonable to use aspiration thrombectomy in patients with a large thrombus burden.
- Distal embolic protection does not appear to protect against no-reflow in the native coronary circulation but is effective in SVGs.
- Patients with hypotension and/or hypoperfusion should be treated with the same approach used in other patients with cardiogenic shock following acute myocardial infarction.
Thank you for your attention!