Review Article

Do We Need Potent Intravenous Antiplatelet Inhibition at the Time of Reperfusion During ST-Segment Elevation Myocardial Infarction

Joseph Allencherril, MD[1], Mahboob Alam, MD[1], Glenn Levine, MD[1], Hani Jneid, MD[1], Dan Atar, MD[2], Robert A. Kloner, MD, PhD[3,4], and Yochai Birnbaum, MD[1]

Abstract

Acute myocardial infarction (MI) is still a large source of morbidity and mortality worldwide. Although early reperfusion therapy has been prioritized in the modern era of percutaneous coronary intervention and thrombolysis, attempts at incremental improvements in clinical outcomes by reducing MI size have not been successful so far. Herein, we review the studies that have evaluated immediate-onset antiplatelet therapy as attempts to improve meaningful clinical outcomes in ST-segment elevation MI (STEMI). Unfortunately, many of the adjunctive pharmacotherapies have proven to be disappointing. Recent studies performed in the background of routine oral administration of $P2Y_{12}$ adenosine receptor inhibitors, which may take several hours to take full effect, and aspirin have largely shown no improvement in outcomes, despite an earlier onset of antiplatelet activity of the investigative agents. Further progress in improving outcomes during STEMI may depend on exploring therapeutics that modulate the pathophysiology of microvascular damage during ischemia–reperfusion injury, a phenomenon whose effects evolve over hours to days. We speculate that the dynamic nature of the no-reflow phenomenon may be an explanation for these disappointing results with the intravenous antiplatelet agents. We hope that appreciation for what has not worked in this domain may direct future research efforts to focus on novel pathways. Myocardial ischemia and reperfusion injury are very much still a lingering issue. Despite significant improvements in door-to-balloon times, rates of in-hospital mortality for STEMI remain unchanged. Outcomes following successfully reperfused STEMI are likely determined by the initial size of myocardial necrosis (ie, cardiomyocyte death during the period of ongoing ischemia), patency of the infarct-related epicardial coronary artery, possible reperfusion injury, the microvascular no-reflow phenomenon, and adverse remodeling after infarction.

Maintaining Myocardial Perfusion During ST-Segment Elevation Myocardial Infarction

Achieving myocardial perfusion after the initial reperfusion (by thrombolysis or primary percutaneous coronary intervention [PCI]) is crucial. It is well established that platelets play a major role in initiating thrombotic (re-)occlusion of the culprit atherosclerotic lesion, stent thrombosis, and reduction of flow in the microcirculation. Therefore, aspirin and other oral antiplatelet agents are routinely used in patients presenting with ST-segment elevation myocardial infarction (STEMI). The perception is that we need additional immediate potent antiplatelet therapy before or immediately after reperfusion.

Antiplatelet therapy aims to limit platelet adhesion and aggregation, the crucial steps in thrombotic coronary occlusion. Aspirin loading (chewable or intravenous) is recommended as soon as possible after the initial encounter with any patient with suspected STEMI, per the most recent STEMI guidelines by the American College of Cardiology/American Heart Association (ACC/AHA) and the European Society of Cardiology (ESC).[1,2,3] Aspirin blocks cyclooxygenase, a mediator of the synthesis of thromboxanes and prostaglandins. Thirty years ago, the Second International Study of Infarct

[1] Section of Cardiology, Baylor College of Medicine, Houston, TX, USA
[2] Department of Cardiology B, Oslo University Hospital, and Institute of Clinical Sciences, University of Oslo, Oslo, Norway
[3] Huntington Medical Research Institute, Pasadena, CA, USA
[4] Division of Cardiovascular Medicine, Department of Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA

Corresponding Author:
Joseph Allencherril, Department of Medicine, Baylor College of Medicine, 1 Baylor Plaza, Houston, TX 77030, USA.
Email: jallencherril@gmail.com

Survival study found that aspirin therapy within the first 24 hours after STEMI onset significantly reduced 5-week vascular and all-cause mortality.[4] After the initial loading dose, subsequent administration of low-dose aspirin (ie, 81 mg daily) is associated with lower gastrointestinal bleeding with the same cardiovascular benefit as higher daily doses.[5,6] Per the 2013 ACC/AHA STEMI guidelines, after an initial aspirin loading dose of 162 to 325 mg, a daily dose of 81 mg is often continued indefinitely for secondary prevention.[7] Likewise, the 2017 ESC STEMI guidelines recommend aspirin administration for all patients without contraindications (class I recommendation).[3]

P2Y$_{12}$ adenosine receptor inhibitors (eg, clopidogrel, prasugrel, ticagrelor) hinder platelet aggregation by blocking adenosine phosphate binding to the platelet receptor P2Y$_{12}$. This inhibits glycoprotein (GP) IIb/IIIa complex activation, which normally assists in cross-linking of fibrin molecules. An oral loading dose of P2Y$_{12}$ receptor inhibitor is to be administered at the time of primary PCI or as early as possible (eg, clopidogrel 600 mg, or preferentially prasugrel 60 mg or ticagrelor 180 mg), with daily therapy to be given for 1 year subsequently in those patients receiving a stent (ie, clopidogrel 75 mg, prasugrel 10 mg, or ticagrelor 90 mg 2 times a day). According to the 2016 ACC/AHA-focused update on dual antiplatelet therapy in patients with coronary artery disease, in patients with non-STEMI (NSTEMI) or STEMI, it is reasonable to use ticagrelor in preference to clopidogrel for maintenance P2Y$_{12}$ inhibitor therapy following PCI; prasugrel may be preferred over clopidogrel for the patient without history of stroke/transient ischemic attack or increased risk of bleeding complications (both class IIa recommendations)[8]; recent guidance from the ESC notes a preference for ticagrelor and prasugrel as well.[3,9]

Other pharmacotherapeutics are used as immediate adjunctive therapy to attenuate thrombosis. The rationale behind intravenous anticoagulation is to prevent extension of the intraluminal thrombosis, which results from atherosclerotic plaque rupture. Anticoagulation is an attempt to mitigate the constant process of thrombus formation. Unfractionated heparin (UFH), with additional bolus as needed, to maintain therapeutic activated clotting time for patients with STEMI undergoing primary PCI, is a class I recommendation by the ACC/AHA task force.[7]

Bivalirudin may also be used in those with or without prior treatment with UFH. No explicit recommendations were given regarding enoxaparin, given its less extensive use in this setting; use of fondaparinux as an anticoagulant by itself is advised against given the risk of catheter thrombosis. The ESC guidelines[3] recommend parenteral anticoagulation for all patients in addition to antiplatelet therapy during primary PCI, with routine use of UFH (class I recommendation) or bivalirudin in patients with heparin-induced thrombocytopenia (class I recommendation).

Oral anticoagulation has also shown promise in long-term clinical outcomes after acute coronary syndrome (ACS). In the phase 3 study of patients with recent ACS, anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome–Thrombolysis in Myocardial Infarction (ATLAS ACS 2-TIMI 51),[10] twice-daily 2.5 mg doses of rivaroxaban led to reduced rates of death from myocardial infarction (MI), stroke, or cardiovascular causes compared to placebo. Among patients with stable atherosclerotic vascular disease, the recent Cardiovascular Outcomes for People Using Anticoagulation Strategies trial,[11] 2.5 mg rivaroxaban twice daily plus aspirin led to a reduced composite end point of cardiovascular death, MI, and stroke with more major bleeding events compared to aspirin alone. The use of rivaroxaban in this setting has been approved by European Medicines Agency but has not yet been approved by the Food and Drug Administration (FDA).

Lack of Adjunctive Benefit With Immediate Antiplatelet Therapy

The importance of long-term dual-antiplatelet therapy (DAPT) after primary PCI for STEMI has been well established. In addition to coronary stent undersizing and active malignancy, the strongest predictor of early and late stent thrombosis is discontinuation of P2Y$_{12}$ adenosine receptor inhibitors at the time of the event (hazard ratio 36.5).[12] Nonresponsiveness to clopidogrel has been linked to a greater risk of subsequent adverse cardiac events.[13,14] Herein, we focus on the failure of *immediate*, intravenous potent antiplatelet therapy to modify clinical outcomes in the setting of STEMI. In the modern era of routine oral aspirin and P2Y$_{12}$ adenosine receptor inhibitor administration, prioritizing immediate antiplatelet effect seems unlikely to lead to additional, meaningful clinical benefit in patients with STEMI as has been demonstrated in a number of clinical trials (Table 1). Table 2 describes landmark studies involving early antiplatelet therapy without the concurrent use of dual antiplatelet therapy.

Glycoprotein IIb/IIIA Inhibitors

GPIIb/IIIa inhibitor administration in isolation (eg, tirofiban) appeared to have salutary effects on the no-reflow area assessed pathologically or by myocardial contrast echocardiography in canine,[25,26] rat,[27] and porcine[28] models; however, the reperfusion times studied were only 1,[27] 2,[28] or 3 hours,[25,26] which would have precluded a robust assessment of the extent of the fully developed no-reflow zone. There have been many attempts over the years to improve clinical outcomes (potentially by mitigating no-reflow and maintaining patency of the infarct related artery) with intravenous antiplatelet and anticoagulation therapies, such as the GPIIb/IIIa inhibitor class. Initial results were quite promising.[29,30] Key results of the trials investigating the use of GPIIb/IIIa inhibitors in patients with STEMI undergoing PCI are summarized in Table 1.

Although these trials, showing improvement in clinical events, illustrate the importance of antiplatelet therapy, the majority were conducted before the introduction of oral P2Y$_{12}$ receptor inhibitors into the routine management of ACSs. More recent trials have not shown much benefit from routine intravenous GPIIb/IIIa inhibitor use in patients receiving aspirin and oral P2Y$_{12}$ receptor inhibitors such as clopidogrel, prasugrel, and ticagrelor.

Table 1. Key Studies Involving Early Antiplatelet Therapy in Patients With STEMI, With the Routine Use of Dual Antiplatelet Therapy.

Trial	Year of Publication	Key Results
EASY RESCUE[15]	2018	In this placebo-controlled, double-blinded trial in STEMI patients with failed thrombolysis undergoing rescue PCI, neither IC nor intravenous (IV) abciximab had significant impact on clinical outcomes (death, myocardial infarction) or secondary measures compared to placebo. All patients received 325 mg aspirin and at least 300 mg of loading dose clopidogrel prior to PCI.
REFLO-STEMI[16]	2016	A group of 247 patients with STEMI undergoing primary PCI with observed TIMI grade 0/1 received bivalirudin anticoagulation and were randomized to (1) primary PCI with IC adenosine 1-2 mg, (2) PCI with IC sodium nitroprusside 250 μg, or (3) standard PCI. A 300 mg loading dose aspirin in addition to either prasugrel (60 mg loading dose) or ticagrelor (180 mg loading dose) were given prior to PCI. Infarct size and MVO were measured by cardiac magnetic resonance at 48-96 hours after PCI, neither of which were decreased by adenosine or nitroprusside. The MACE were increased at 30 days and 6 months in the adenosine arm.
BRIGHT[17]	2015	In a trial of patients with STEMI undergoing primary PCI, there were no significance differences in major adverse cardiac or cerebral events in groups receiving either bivalirudin anticoagulation with a median 3-hour post-PCI infusion, heparin alone, or heparin plus tirofiban. Patients received oral loading dose prior to PCI of 300 mg aspirin if not on long-term aspirin (otherwise 100-300 mg) and 300 to 600 mg clopidogrel if not on long-term clopidogrel.
ATLANTIC[18]	2016	Prehospital loading with ticagrelor in patients with STEMI did not improve pre-PCI coronary reperfusion compared to loading in the catheterization laboratory. The median time difference in administration was 31 minutes. Patients were anticoagulated.
HORIZONS-AMI[19]	2008	Bivalirudin anticoagulation, compared with heparin and GPIIb/IIIa inhibitor therapy (abciximab, eptifibatide, or tirofiban at operator discretion) resulted in reduced 30-day cardiac mortality (1.8% vs 2.9%) in patients with STEMI undergoing primary PCI. Clopidogrel loading before catheterization was performed for all patients.
EUROMAX[20]	2013	In a more contemporary setting, bivalirudin started during transport improved 30-day major bleeding and stent thrombosis compared to heparin and GPIIb/IIIA inhibitor (bailout use allowed with large thrombus burden or angiographically visualized no-reflow) in patients with STEMI undergoing primary PCI.
ADMIRAL[21,22]	2001, 2005	Early abciximab use prior to primary PCI improved the primary end point (composite of death, reinfarction, or urgent revascularization of the target vessel) at 30 days as well as 6 months compared to placebo in those with STEMI. All patients received aspirin.[21] First-generation $P2Y_{12}$ adenosine receptor inhibitors ticlopidine 250 mg twice daily without a loading dose was administered for 30 days immediately after PCI in both arms. In a 3-year follow-up, rates of death, reinfarction, recurrent ischemia, and all-cause mortality were still reduced.[22]
REOPEN-AMI[23]	2013	240 patients with STEMI receiving primary PCI with TIMI 0/1 flow grade were given either IC adenosine (120 μg as fast bolus followed by 2 mg over 2 minutes), nitroprusside (60 μg fast bolus, followed by 100 μg over 2 minutes) or saline infusion. All primary PCI patients received aspirin (250 mg IV), clopidogrel (600 mg) with IV bolus abciximab and heparin given prior to PCI. The primary end point measured was ST segment resolution (STR) on EKG at 90 minutes post-PCI. Adenosine, but not nitroprusside, improved STR, although angiographic MVO (TIMI flow grade <2 or 3 and myocardial blush grade <2 and 30-day MACE were not significantly different between groups. However, follow-up at 1 year of REOPEN-AMI data[24] demonstrated lower incidence of CHF, MI, and death. Improved remodeling of the LV (assessed by echocardiography) was observed with the adenosine arm but not the nitroprusside arm. Follow-up at 1 year of REOPEN-AMI data[24] demonstrated lower incidence of CHF, MI, and death. Improved remodeling of the LV (assessed by echocardiography) was observed with the adenosine arm but not the nitroprusside arm.

Abbreviations: CHF, congestive heart failure; GPIIb/IIIA, glycoprotein IIb/IIIa; IC, intracoronary; IV, intravenous; LV, left ventricle; MACE, major adverse cardiac events; MI, myocardial infarction; MVO, microvascular obstruction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.

With clopidogrel loading done before catheterization in all Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction study trial patients, heparin and GPIIb/IIIa inhibitor therapy (abciximab, eptifibatide, or tirofiban at operator discretion) underperformed bivalirudin anticoagulation with respect to 30-day cardiac mortality in patients undergoing primary PCI.[19] Similarly, the European Ambulance Acute Coronary Syndrome Angiography trial compared heparin and GPIIb/IIIA inhibitor (bailout use allowed with large thrombus burden or angiographically visualizing

no-reflow) to bivalirudin anticoagulation started en route to the catheterization laboratory. The heparin and GPIIb/IIIa inhibitor arm underperformed with respect to 30-day major bleeding and stent thrombosis rates in patients with STEMI undergoing primary PCI.[20] A trial of acute patients with STEMI undergoing primary PCI showed no significant differences in major adverse cardiac or cerebral events in groups receiving either bivalirudin anticoagulation with a median 3-hour post-PCI infusion, heparin alone, or heparin plus tirofiban.[17] In a placebo-controlled, double-blinded randomized controlled trial

Table 2. Key Studies Involving Early Antiplatelet Therapy in Patients With STEMI, Without the Use of Dual Antiplatelet Therapy.

RAPPORT[64]	1998	Abciximab use during primary PCI for STEMI led to a reduction in 3-day mortality, reinfarction, and urgent target vessel revascularization although the 6-month primary end point remained unaffected.
ACE[65]	2003	In this randomized trial, abciximab use reduced the primary end point (death, reinfarction, target vessel revascularization, and stroke) at one month. At 6-month follow-up, there was a cumulative decrease in mortality for the abciximab group compared to the placebo group. Patients received 325 mg aspirin orally or 250 mg IV prior to catheterization.
ISAR-2[66]	2000	Patients undergoing stenting within 48 hours of STEMI onset were assigned to receive heparin or abciximab with reduced-dose heparin. The abciximab group exhibited a reduction in the 30-day composite of death, reinfarction, and target lesion revascularization; however, at one-year follow-up, there was no significant difference between groups. All patients received 500 mg aspirin prior to catheterization.
CADILLAC[67]	2002	In a 2-by-2 factorial design, patients with STEMI were assigned to undergo percutaneous transluminal angioplasty (PTCA) alone, PTCA with abciximab, stenting alone, or stenting with abciximab. There were no significant differences among the groups with regard to rates of mortality, reinfarction, or stroke. Patients received 325 mg of chewable aspirin or 250 mg IV before catheterization.
AMISTAD I[45]	1999	Administration of adenosine (70 µg/kg/min for 3 hours) within 6 hours of the onset of STEMI, reduced infarct size assessed by Tc-99 m sestamibi SPECT compared to placebo infusion in patients undergoing thrombolysis (streptokinase or alteplase), by 6 ± 1 days after enrollment. No statistically significant reduction in hard clinical outcomes was observed.
AMISTAD II[46]	2005	Adenosine infusion during evolving anterior STEMI (receiving thrombolysis or primary angioplasty within 6 hours of symptoms) did not improve clinical outcomes (new CHF onset >24 hours post-randomization, CHF rehospitalization, all-cause mortality at 6 months). Patients were randomly assigned to receive adenosine at 70 µg/kg/min, 50 µg/kg/min, or placebo infusion within 15 minutes of reperfusion in a 1:1:1 fashion. A dose–response relationship emerged with final median infarct size despite a nonsignificant trend toward reduced median infarct size in the pooled adenosine intervention group.

Abbreviations: CHF, congestive heart failure; GPIIb/IIIA, glycoprotein IIb/IIIa; IV, intravenous; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; SPECT, single-photon emission computed tomography.

in patients with STEMI with failed thrombolysis undergoing rescue PCI, the EASY RESCUE investigators found that neither intracoronary (IC) nor intravenous abciximab had significant impact on clinical outcomes (death, MI) or secondary measures compared to placebo. All patients received 325 mg aspirin and at least 300 mg of loading dose clopidogrel prior to PCI.[15] The 2017 ESC task force on the management of STEMI offers only a class IIb recommendation for GPIIb/IIIA receptor inhibitor use as bailout therapy in cases of angiographic evidence of massive thrombus burden, thrombotic complication, or no reflow.[3] Likewise, the 2013 ACC/AHA task force gives a class IIa recommendation for GPIIb/IIIA receptor inhibitors in conjunction with UFH or bivalirudin in select patients at the time of PCI (with or without stenting or prior clopidogrel loading).[7]

In ACS, routine upstream initiation of GPIIb/IIIa inhibitors, compared to the deferred selective use of the drugs, did not demonstrate a statistically significant difference in composite ischemia although there was a significant increase in major bleeding. Furthermore, GPIIb/IIa inhibitor therapy and anterior wall MI have been linked to the occurrence of intramyocardial hemorrhage, which is associated with larger infarctions with poor left ventricle (LV) functional recovery compared to those with microvascular obstruction (MVO) alone.[31] Microvascular obstruction is an independent predictor of cardiac death and major adverse cardiac events (MACE).[32]

P2Y$_{12}$ Adenosine Receptor Inhibitors

Oral administration of P2Y$_{12}$ inhibitor is standard of care in the modern era of ACS management. The efficacy of oral P2Y$_{12}$ inhibition has been demonstrated in multiple key clinical trials.

A 600-mg loading dose of clopidogrel brings about adequate inhibition of platelet function after approximately 6 hours.[33] The Clopidogrel as Adjunctive Reperfusion Therapy—TIMI 28 group studied 3491 patients (18-75 years of age) presenting within 12 hours of STEMI onset.[34] Participants were assigned to either placebo or clopidogrel (300 mg loading dose with 75 mg daily thereafter); they received fibrinolytic therapy, aspirin and heparin (when appropriate).[35] The rates of the primary end point (composite of angiographic occlusion of the infarct-related artery or death or recurrent MI preceding angiography) were reduced to 15.0% in the clopidogrel group compared to 21.7% in the placebo group ($P < .001$). At 30 days, clopidogrel therapy was associated with reduced composite end point of cardiovascular death, recurrent ischemia necessitating urgent revascularization, or recurrent MI (11.6% vs 14.1%; $P = .03$).

More potent oral antiplatelet agents have also been evaluated. In the study of Platelet Inhibition and Patient Outcomes (PLATO) trial,[36] 18 624 patients admitted with suspected ACS (37.5% with persistent ST Segment Elevation [STE]) were studied with treatment with ticagrelor (180 mg loading dose, 90 mg twice daily thereafter) and clopidogrel (300-600 mg loading dose, 75 mg daily thereafter). At 12 months posttreatment, the composite of death from vascular causes, MI, or stroke occurred in 9.8% of patients in the ticagrelor arm compared with 11.7% of in the clopidogrel arm ($P < .001$). Results of a substudy of patients with STE or left bundle branch block were similar to those of the overall trial.[37]

Similarly, the TRial to assess Improvement in Therapeutic Outcomes by optimizing platelet inhibitioN with prasugrel—TIMI 38 (TRITON-TIMI)[38] demonstrated the benefits of

prasugrel compared to clopidogrel in patients with STEMI. The larger effect size (3.0%) observed in the TRITON-TIMI study is likely given that PCI was carried out several days after the sentinel event and much of benefit would be observed in the first 24 hours of presentation; however, in the PLATO trial, it is difficult to distinguish between the sentinel MI and periprocedural MI as patients presented with evolving MI.

Cangrelor, an IV inhibitor of the $P2Y_{12}$ adenosine receptor, was evaluated with the expectation of improved clinical outcomes, given its rapid onset compared to clopidogrel, but trial results appear to be another failure of adjunctive pharmacological therapies to improve ischemic cardiovascular disease outcomes.

The Cangrelor versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition (CHAMPION) PLAT-FORM[39] and CHAMPION PCI[40] trials did not demonstrate clinical superiority of intravenous cangrelor over oral clopidogrel in patients with NSTEMI, STEMI, or stable angina pectoris undergoing PCI. In both randomized controlled trials, cangrelor was infused intravenously throughout PCI or for 2 hours, whichever period was longer. In the later CHAMPION PHOENIX study (stable angina 57.0%, NSTEMI 25.4%, STEMI 17.6% of the patients),[41] cangrelor reduced the rate of ischemic events compared to clopidogrel alone in patients undergoing urgent or elective PCI. However, the effect size was small: the absolute risk reduction of the primary end point, a composite of death, MI, ischemic-driven revascularization, and stent thrombosis at 48 hours post-randomization, was 1.2% in the cangrelor arm compared to the control arm. There was a 0.1% absolute risk reduction ($P = .02$) in MI at 48 hours post-randomization. All-cause mortality and cardiovascular mortality were not statistically different between both arms.

Nevertheless, the United States FDA approved cangrelor in June 2015 as adjunctive therapy to PCI in patients with inadequate prior treatment with a $P2Y_{12}$ receptor inhibitors and who were not to receive GPIIb/IIIa/inhibitors in the planned clinical course (GPIIb/IIIa). The 2017 ESC STEMI guidelines suggest cangrelor may be considered in patients not receiving pretreatment with oral $P2Y_{12}$ receptor inhibitors at the time of PCI or those who are considered unable to absorb oral agents.[3]

In the CHAMPION PLATFORM trial, over 5000 patients (NSTEMI, 59.4% unstable angina 35.4%, stable angina 5.2% of the patients) were assigned randomly to receive either placebo or cangrelor infusion 30 minutes prior to PCI. A loading dose of 600 mg of clopidogrel was administered to both study arms following the procedure. The study failed to show a significant difference in the primary composite end point (death, MI, or ischemia-drive revascularization).[39] In the CHAMPION PCI trial, over 8000 patients (11% STEMI, 49.2% NSTEMI, 24.7% unstable angina, 15.1% stable angina) were randomly assigned to receive either 600 mg clopidogrel or IV cangrelor infusion 30 minutes before PCI. The same primary composite end point (death, MI, ischemia-drive revascularization) was measured and found to not significantly differ between the 2 intervention arms.[40]

Notably, the ATLANTIC trial demonstrated that prehospital oral loading with ticagrelor in patients with STEMI did not improve pre-PCI coronary reperfusion compared to loading in the catheterization laboratory. However, the median time difference in administration between the prehospital and the control arm was only 31 minutes.[18]

The ACC/AHA Task Force recommend the administration of a loading dose of a $P2Y_{12}$ inhibitor (ie, clopidogrel 600 mg, prasugrel 60 mg, or ticagrelor 180 mg) in addition to aspirin 162 to 325 mg in the setting of STEMI[7]; a recent guideline-focused update reveals a preference for prasugrel or ticagrelor for maintenance DAPT therapy. Similarly, European guidelines advise administration of a potent $P2Y_{12}$ inhibitor (ticagrelor or prasugrel) or clopidogrel, if these are unavailable, before (or at least at the time of) PCI, in the absence of contraindications. Of note, the Task Force did not insist on $P2Y_{12}$ inhibitor loading prior to PCI. The risk of bleeding relating to coronary artery bypass graft surgery has been described in loading with clopidogrel,[42] prasugrel,[43] and ticagrelor.[36] Withholding $P2Y_{12}$ inhibition may be desired if surgery is anticipated, as in cases of previously discerned coronary anatomy, clinically significant valvular disease, or those suffering mechanical complications of MI.

Adenosine

Adenosine, a purine nucleoside, primarily elicits smooth muscle relaxation in the coronary microcirculation, but it also exerts antiplatelet effects. The binding of this metabolite to G-protein-coupled adenosine receptors leads to increased intracellular cyclic adenosine monophosphate, a potent platelet activity inhibitor.[44]

The administration of adenosine as adjunctive therapy to reperfusion during STEMI was first evaluated in the Acute Myocardial Infarction STudy of ADenosine (AMISTAD) trials (Table 1). In the AMISTAD I trial,[45] administration of adenosine (70 µg/kg/min for 3 hours) within 6 hours of the onset of STEMI reduced infarct size assessed by Tc-99 m sestamibi single-photon emission computed tomography compared to placebo infusion in patients undergoing thrombolysis (streptokinase or alteplase), by 6 ± 1 days after enrollment. A 33% relative reduction in infarct size was seen with adenosine ($P = .03$), although no statistically significant reduction in hard clinical outcomes was observed.

In the AMISTAD II trial,[46] adenosine IV infusion during evolving anterior STEMI (thrombolysis or primary angioplasty within 6 hours of symptoms) did not improve clinical outcomes (new congestive heart failure [CHF] onset >24 hours postrandomization, CHF rehospitalization, all-cause mortality at 6 months). Patients were randomly assigned to receive adenosine infusion at 70 µg/kg/min, 50µg/kg/min, or placebo infusion within 15 minutes of reperfusion in a 1:1:1 fashion. A dose–response relationship emerged with final median infarct size: 27% (of left ventricle) in the placebo group, 23% with the low-dose group ($P = $ nonsignificant vs placebo) and 11% with the high-dose group ($P = .023$ vs placebo infusion), despite a

nonsignificant trend toward reduced median infarct size in the pooled adenosine intervention group. Post hoc analysis of the AMISTAD II data revealed that 3-hour adenosine infusion given when reperfusion was performed within approximately 3 hours of onset of ongoing anterior STEMI improved survival at 1 month and 6 months in addition to heart failure occurrence and heart failure rehospitalization at 6 months.[47]

In the modern era, the use of adenosine as an agent to mitigate no-reflow during STEMI was examined in the Intracoronary Nitroprusside Versus Adenosine in Acute Myocardial Infarction (REOPEN-AMI) trial[23] (Table 1), which sought to determine whether IC adenosine or sodium nitroprusside after thrombus aspiration improve outcomes over thrombus aspiration alone. A total of 240 patients with STEMI having TIMI 0/1 flow grade were given adenosine, nitroprusside, or saline infusion. Aspirin and clopidogrel (600 mg) were given in the emergency department with IV abciximab (0.25 mg/kg bolus, 12-hour infusion thereafter) and heparin (5000 IU) bolus given prior to PCI. The primary end point measured was ST-segment resolution on the electrocardiogram at 90 minutes post-PCI. Adenosine, but not nitroprusside, improved ST-segment resolution, although angiographic MVO (TIMI flow grade <2 or 3 and myocardial blush grade <2) and MACE at 30 days were not significantly different among the groups. Follow-up up at 1 year of the REOPEN-AMI data[24] demonstrated lower incidence of heart failure, MI, and death with adenosine. Improved remodeling of the LV (assessed by echocardiography) was observed with the adenosine arm but not the nitroprusside arm.

In a study of 90 patients with STEMI, 3-hour continuous infusion of adenosine (70 μg/kg/min) reduced the rate of no-reflow compared to a lower adenosine dose (50 μg/kg/min) and control arms. No reflow was assessed by the ratio of the sum of ST-segment elevation in all 12 surface leads pre-PCI to the same sum counted post-PCI.[48] Left Ventricular Ejection Fraction (LVEF), assessed by echocardiography, was improved while clinical outcomes (heart failure occurrence, nonfatal MI, noncardiac death) were not impacted at 6 months postintervention. One caveat is that the permitted use of nitroprusside and verapamil in study patients clouds the isolation of the effect adenosine on its own.

Direct evidence of the effect of adenosine on delayed no-reflow, as assessed by cardiac magnetic resonance, has been scarce. In a recent trial,[16] patients with STEMI undergoing primary PCI with observed TIMI grade 0/1 flow received bivalirudin anticoagulation and were randomized to (1) primary PCI with IC adenosine 1 to 2 mg, (2) PCI with IC sodium nitroprusside 250 μg, or (3) standard PCI alone. Loading doses of aspirin as well as prasugrel or ticagrelor were given pre-PCI. However, infarct size and MVO assessed at 48 to 96 hours post-PCI by cardiac magnetic resonance were not decreased by adenosine or nitroprusside. In fact, MACEs were increased at 30 days and 6 months in the adenosine arm. If adenosine is working primarily through an antiplatelet mechanism, it is possible that its effects are masked in a background of aspirin and P2Y$_{12}$ receptor inhibitor loading.

Adenosine seems to be one of few intravenous therapies to attenuate final infarct size in humans; the mechanism behind this observation—whether related to antiplatelet properties or direct cardioprotective effects has not been clarified. Although meta-analyses of adenosine therapy in the setting of STEMI have offered conflicting results on hard clinical outcomes, all analyses suggest possible improvement in surrogate measures of microvascular dysfunction (ie, TIMI grade flow and ST-segment resolution).[49-51]

Oral and Intravenous Antiplatelet Agents

Full-dose aspirin therapy on its own does not seem to prevent the no-reflow phenomenon given that most patients undergoing reperfusion in the setting of STEMI have received aspirin yet still evidence a high rate of no-reflow,[52] an outcome that we hypothesize is due to the underlying importance of delayed no-reflow during the postinfarct period. In the canine model of coronary artery occlusion, tissue plasminogen activator,[53] streptokinase,[54] and dabigatran,[55] have all failed to improve no-reflow when assessed by the thioflavin S fluorescent dye technique and the microspheres technique in the laboratory. In humans, the narrow set of pharmacological and nonpharmacological interventions that potentially attenuate no-reflow and microvascular disease have been detailed before.[56]

Immediately after restoration of coronary flow, hyperemic myocardial blood flow occurs. Imaging performed soon after restoration of coronary blood flow likely underestimates the size of the no-reflow zone,[57-59] as the area changes dynamically due to myocardial edema and vasospasm during the first 3 hours. The no-reflow zone may be fully developed as late as 48 hours postreperfusion as active changes in resting myocardial perfusion will have abated, so this may be a more ideal time to assess its extent.[58] By the time that delayed no-reflow develops and effective platelet inhibition are probably needed, blood concentrations of the oral antiplatelet agents are sufficient to exert therapeutic effects. Alternatively, the effects of the antiplatelet therapy is not on the no-reflow phenomenon. These agents may affect epicardial artery patency. Again, with the background of anticoagulation and aspirin, full effect might be needed only a few hours after reperfusion and can safely and effectively be achieved by oral therapy. It is unclear whether IV antiplatelet agents (eg, GPIIb/IIIa inhibitors and cangrelor), on top of aspirin loading and anticoagulation therapy, are truly effective against distal embolization of plaque debris.

Notably, the fact that the immediate IV agents do not have dramatic clinical effect in a background of aspirin and P2Y$_{12}$ receptor inhibition may indicate that they are not effective, or that the issue of provoked thromboembolization (ie, "immediate" no-reflow), per se, is not as important as commonly believed. If indeed the full antiplatelet effect is needed only a few hours after restoration of macrovascular coronary flow and not immediately after

reperfusion, oral agents administered at the time of PCI likely suffice.

Future Directions

Experimental models have failed to show a benefit to thrombolytic therapy or anticoagulation after reperfusion in reduction of the no-reflow zone.[55] Vasodilators (adenosine, nitroprusside, nitroglycerin, calcium channel blockers) have shown different degrees of mitigating clinical no-reflow.[56] Adenosine, which also demonstrates antiplatelet activity, seems to have had some benefit in mitigating no-reflow, but aggregated data are conflicting and less ideal markers of the phenomenon (ie, ST-segment resolution) were used in its assessment during key studies.[49-51] Mechanical methods directed at thrombi have been met with disappointment, underlining the lower impact that immediate no-reflow plays in the perireperfusion period. Distal protection devices (ie, filters and balloons) have not shown any clinical benefit in mitigating no-reflow during STEMI.[60] Rheolytic thrombectomy may actually potentiate no-reflow in some patients.[61] Although aspiration thrombectomy is widely used, its use does not seem to reduce post-STEMI clinical measures (30-day post-MI mortality, reinfarction, and stroke) despite improved early markers of reperfusion (ST-segment resolution and angiographic outcome).[62] A more recent meta-analysis of long-term outcomes reported similar findings, with an actual increased stroke risk in patients undergoing the procedure.[63]

We believe that the failure of early, full-dose intravenous antiplatelet therapies to demonstrate strong superiority over slower onset oral agents underlines the importance of delayed microvascular damage, which evolves over several hours after coronary reperfusion. Early spontaneous or provoked thromboembolization of plaques does not seem to drive as much of the microvascular damage and myocardial perfusion deficits in the postinfarct period, and oral antithrombotic therapy (namely, aspirin and $P2Y_{12}$ inhibitor) is likely sufficient, as inhibition of platelet aggregation takes place within a couple of hours.

Thomas Edison, on inventing the light bulb, is believed to have said, "I have not failed. I've just found 10,000 ways that won't work." In examining what has not worked, we may find an avenue to approach future therapeutics in this domain.

Author Contributions

All the authors contributed to conception, design, acquisition, analysis, and interpretation; drafted the manuscript; critically revised the manuscript; gave final approval; and agrees to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

ORCID iD

Joseph Allencherril, MD ![ORCID] https://orcid.org/0000-0003-4940-0374

References

1. Menees DS, Peterson ED, Wang Y, et al. Door-to-Balloon time and mortality among patients undergoing primary PCI. *N Engl J Med*. 2013;369(10):901-909. doi:10.1056/NEJMoa1208200.

2. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction. *J Am Coll Cardiol*. 2013;61(4):e78-e140. doi:10.1016/j.jacc.2012.11.019.

3. Ibanez B, James S, Agewall S, et al. 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J*. 2018;39(2):119-177. doi:10.1093/eurheartj/ehx393.

4. . Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. *Lancet (London, England)*. 1988;2(8607):349-360. http://www.ncbi.nlm.nih.gov/pubmed/2899772. Accessed July 28, 2018.

5. Xian Y, Wang TY, McCoy LA, et al. Association of discharge aspirin dose with outcomes after acute myocardial infarction: insights from the Treatment with ADP Receptor Inhibitors: Longitudinal Assessment of Treatment Patterns and Events after Acute Coronary Syndrome (TRANSLATE-ACS) Study. *Circulation*. 2015;132(3):174-181. doi:10.1161/CIRCULATIONAHA.114.014992.

6. CURRENT-OASIS7 Investigators Mehta SR, Bassand J-P, et al. Dose comparisons of clopidogrel and aspirin in acute coronary syndromes. *N Engl J Med*. 2010;363(10):930-942. doi:10.1056/NEJMoa0909475.

7. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013;127(4):e362-e425. doi:10.1161/CIR.0b013e3182742cf6.

8. Levine GN, Eric Bates CR, Bittl JA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2016;68(10):1082-1115. doi:10.1016/j.jacc.2016.03.513.

9. Valgimigli M, Bueno H, Byrne RA, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS. *Eur Heart J*. 2018;39(3):213-260. doi:10.1093/eurheartj/ehx419.

10. Mega JL, Braunwald E, Wiviott SD, et al. Rivaroxaban in patients with a recent acute coronary syndrome. *N Engl J Med*. 2012;366(1):9-19. doi:10.1056/NEJMoa1112277.

11. Eikelboom JW, Connolly SJ, Bosch J, et al. Rivaroxaban with or without aspirin in stable cardiovascular disease. *N Engl J Med*. 2017;377(14):1319-1330. doi:10.1056/NEJMoa1709118.

12. van Werkum JW, Heestermans AA, Zomer AC, et al. Predictors of coronary stent thrombosis: the Dutch stent thrombosis registry. *J Am Coll Cardiol*. 2009;53(16):1399-1409. doi:10.1016/j.jacc. 2008.12.055.

13. Marcucci R, Gori AM, Paniccia R, et al. Cardiovascular death and nonfatal myocardial infarction in acute coronary syndrome patients receiving coronary stenting are predicted by residual platelet reactivity to ADP detected by a point-of-care assay: a 12-month follow-up. *Circulation*. 2009;119(2):237-242. doi:10.1161/CIRCULATIONAHA.108.812636.

14. Matetzky S, Shenkman B, Guetta V, et al. Clopidogrel resistance is associated with increased risk of recurrent atherothrombotic events in patients with acute myocardial infarction. *Circulation*. 2004;109(25):3171-3175. doi:10.1161/01.CIR.0000130846. 46168.03.

15. Bertrand OF, Larose É, Bagur R, et al. A randomized double-blind placebo-controlled study comparing intracoronary versus intravenous abciximab in patients with ST-elevation myocardial infarction undergoing transradial rescue percutaneous coronary intervention after failed thrombolysis. *Am J Cardiol*. 2018; 122(1):47-53. doi:10.1016/j.amjcard.2018.03.007.

16. Nazir SA, Khan JN, Mahmoud IZ, et al. The REFLO-STEMI (REperfusion facilitated by LOcal adjunctive therapy in ST-elevation myocardial infarction) trial: a randomised controlled trial comparing intracoronary administration of adenosine or sodium nitroprusside with control for attenuation of mi. *Effic Mech Eval*. 2016;3(9). doi:10.3310/eme03090.

17. Han Y, Guo J, Zheng Y, et al. Bivalirudin vs heparin with or without tirofiban during primary percutaneous coronary intervention in acute myocardial infarction: the BRIGHT randomized clinical trial. *JAMA*. 2015;313(13):1336-1346. doi:10.1001/jama.2015.2323.

18. Montalescot G, van 't Hof AW, Lapostolle F, et al. Prehospital ticagrelor in ST-segment elevation myocardial infarction. *N Engl J Med*. 2014;371(11):1016-1027. doi:10.1056/NEJMoa1407024.

19. Stone GW, Witzenbichler B, Guagliumi G, et al. Bivalirudin during primary PCI in acute myocardial infarction. *N Engl J Med*. 2008;358(21):2218-2230. doi:10.1056/NEJMoa0708191.

20. Steg PG, van 't Hof A, Hamm CW, et al. Bivalirudin started during emergency transport for primary PCI. *N Engl J Med*. 2013;369(23):2207-2217. doi:10.1056/NEJMoa1311096.

21. Montalescot G, Barragan P, Wittenberg O, et al. Platelet glycoprotein IIb/IIIa inhibition with coronary stenting for acute myocardial infarction. *N Engl J Med*. 2001;344(25):1895-1903. doi: 10.1056/NEJM200106213442503.

22. Admiral Investigators. Three-year duration of benefit from abciximab in patients receiving stents for acute myocardial infarction in the randomized double-blind ADMIRAL study. *Eur Heart J*. 2005;26(23):2520-2523. doi:10.1093/eurheartj/ehi620.

23. Niccoli G, Rigattieri S, De Vita MR, et al. Open-Label, randomized, placebo-controlled evaluation of intracoronary adenosine or nitroprusside after thrombus aspiration during primary percutaneous coronary intervention for the prevention of microvascular obstruction in acute myocardial infarction. *JACC Cardiovasc Interv*. 2013;6(6):580-589. doi:10.1016/j.jcin.2013.02.009.

24. Niccoli G, Spaziani C, Crea F, REOPEN-AMI Investigators. Left ventricular remodeling and 1-year clinical follow-up of the REOPEN-AMI Trial. *J Am Coll Cardiol*. 2014;63(14): 1454-1455. doi:10.1016/j.jacc.2013.10.042.

25. Kunichika H, Ben-Yehuda O, Lafitte S, Kunichika N, Peters B, DeMaria AN. Effects of glycoprotein IIb/IIIa inhibition on microvascular flow after coronary reperfusion. *J Am Coll Cardiol*. 2004;43(2):276-283. doi:10.1016/j.jacc.2003.08.040.

26. Kingma JG, Plante S, Bogaty P. Platelet GPIIb/IIIa Receptor blockade reduces infarct size in a canine model of ischemia-reperfusion. *J Am Coll Cardiol*. 2000;36(7):2317-2324. doi:10.1016/S0735-1097(00)01016-0.

27. Yang YJ, Zhao JL, You SJ, et al. Different effects of tirofiban and aspirin plus clopidogrel on myocardial no-reflow in a mini-swine model of acute myocardial infarction and reperfusion. *Heart*. 2006;92(8):1131-1137. doi:10.1136/hrt.2005.077164.

28. Liu X, Tao G. Effects of tirofiban on the reperfusion-related no-reflow in rats with acute myocardial infarction. *J Geriatr Cardiol*. 2013;10(1):52-58. doi:10.3969/J.ISSN.1671-5411.2013.01.009.

29. De Luca G, Suryapranata H, Stone GW, et al. Abciximab as adjunctive therapy to reperfusion in acute ST-segment elevation myocardial infarction. *JAMA*. 2005;293(14): 1759-1765. doi:10.1001/jama.293.14.1759.

30. Boersma E, Harrington RA, Moliterno DJ, et al. Platelet glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: a meta-analysis of all major randomised clinical trials. *Lancet*. 2002; 359(9302):189-198. doi:10.1016/S0140-6736(02)07442 -1.

31. Amier RP, Tijssen RYG, Teunissen PFA, et al. Predictors of intramyocardial hemorrhage after reperfused ST-segment elevation myocardial infarction. *J Am Heart Assoc*. 2017;6(8): e005651. doi:10.1161/JAHA.117.005651.

32. van Kranenburg M, Magro M, Thiele H, et al. Prognostic value of microvascular obstruction and infarct size, as measured by CMR in STEMI patients. *JACC Cardiovasc Imaging*. 2014;7(9): 930-939. doi:10.1016/j.jcmg.2014.05.010.

33. Montalescot G, Sideris G, Meuleman C, et al. A Randomized comparison of high clopidogrel loading doses in patients with Non–ST-segment elevation acute coronary syndromes. *J Am Coll Cardiol*. 2006;48(5):931-938. doi:10.1016/j.jacc.2006.04.090.

34. Sabatine MS, Cannon CP, Gibson CM, et al. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. *N Engl J Med*. 2005;352(12): 1179-1189. doi:10.1056/NEJMoa050522.

35. Chen ZM, Jiang LX, Chen YP, et al. Addition of clopidogrel to aspirin in 45 852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet*. 2005;366(9497): 1607-1621. doi:10.1016/S0140-6736(05)67660-X.

36. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2009;361(11):1045-1057. doi:10.1056/NEJMoa0904327.

37. Steg PG, James S, Harrington RA, et al. Ticagrelor versus clopidogrel in patients with ST-elevation acute coronary syndromes intended for reperfusion with primary percutaneous coronary intervention: a Platelet Inhibition and Patient Outcomes (PLATO)

trial subgroup analysis. *Circulation*. 2010;122(21):2131-2141. doi:10.1161/CIRCULATIONAHA.109.927582.

38. Montalescot G, Wiviott SD, Braunwald E, et al. Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): double-blind, randomised controlled trial. *Lancet*. 2009;373(9665):723-731. doi:10.1016/S0140-6736(09)60441-4.

39. Bhatt DL, Lincoff AM, Gibson CM, et al. Intravenous platelet blockade with cangrelor during PCI. *N Engl J Med*. 2009;361(24):2330-2341. doi:10.1056/NEJMoa0908629.

40. Harrington RA, Stone GW, McNulty S, et al. Platelet inhibition with cangrelor in patients undergoing PCI. *N Engl J Med*. 2009;361(24):2318-2329. doi:10.1056/NEJMoa0908628.

41. Bhatt DL, Stone GW, Mahaffey KW, et al. Effect of platelet inhibition with cangrelor during PCI on ischemic events. *N Engl J Med*. 2013;368(14):1303-1313. doi:10.1056/NEJMoa1300815.

42. Fox KAA, Mehta SR, Peters R, et al. Benefits and risks of the combination of clopidogrel and aspirin in patients undergoing surgical revascularization for non-ST-elevation acute coronary syndrome: the clopidogrel in unstable angina to prevent recurrent ischemic events (CURE) Trial. *Circulation*. 2004;110(10):1202-1208. doi:10.1161/01.CIR.0000140675.85342.1B.

43. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2007;357(20):2001-2015. doi:10.1056/NEJMoa0706482.

44. Johnston-Cox HA, Yang D, Ravid K. Physiological implications of adenosine receptor-mediated platelet aggregation. *J Cell Physiol*. 2011;226(1):46-51. doi:10.1002/jcp.22379.

45. Mahaffey KW, Puma JA, Barbagelata NA, et al. Adenosine as an adjunct to thrombolytic therapy for acute myocardial infarction: results of a multicenter, randomized, placebo-controlled trial: the Acute Myocardial Infarction STudy of ADenosine (AMISTAD) trial. *J Am Coll Cardiol*. 1999;34(6):1711-1720. http://www.ncbi.nlm.nih.gov/pubmed/10577561. Accessed November 1, 2018.

46. Ross AM, Gibbons RJ, Stone GW, Kloner RA, Alexander RW AMISTAD-II investigators. A randomized, double-blinded, placebo-controlled multicenter trial of adenosine as an adjunct to reperfusion in the treatment of acute myocardial infarction (AMISTAD-II). *J Am Coll Cardiol*. 2005;45(11):1775-1780. doi:10.1016/j.jacc.2005.02.061.

47. Kloner RA, Forman MB, Gibbons RJ, Ross AM, Alexander RW, Stone GW. Impact of time to therapy and reperfusion modality on the efficacy of adenosine in acute myocardial infarction: the AMISTAD-2 trial. *Eur Heart J*. 2006;27(20):2400-2405. doi:10.1093/eurheartj/ehl094.

48. Zhang H, Tian N-L, Hu Z-Y, et al. Three hours continuous injection of adenosine improved left ventricular function and infarct size in patients with ST-segment elevation myocardial infarction. *Chin Med J (Engl)*. 2012;125(10):1713-1719. http://www.ncbi.nlm.nih.gov/pubmed/22800889. Accessed November 1, 2018.

49. Gao Q, Yang B, Guo Y, Zheng F. Efficacy of adenosine in patients with acute myocardial infarction undergoing primary percutaneous coronary intervention: a PRISMA-compliant meta-analysis. *Medicine (Baltimore)*. 2015;94(32): e1279. doi:10.1097/MD.0000000000001279.

50. Navarese EP, Buffon A, Andreotti F, et al. Adenosine improves post-procedural coronary flow but not clinical outcomes in patients with acute coronary syndrome: a meta-analysis of randomized trials. *Atherosclerosis*. 2012;222(1):1-7. doi:10.1016/j.atherosclerosis.2011.11.001.

51. Polimeni A, De Rosa S, Sabatino J, Sorrentino S, Indolfi C. Impact of intracoronary adenosine administration during primary PCI: a meta-analysis. *Int J Cardiol*. 2016;203: 1032-1041. doi:10.1016/j.ijcard.2015.11.086.

52. de Waha S, Patel MR, Granger CB, et al. Relationship between microvascular obstruction and adverse events following primary percutaneous coronary intervention for ST-segment elevation myocardial infarction: an individual patient data pooled analysis from seven randomized trials. *Eur Heart J*. 2017;38(47):3502-3510. doi:10.1093/eurheartj/ehx414.

53. Kloner RA, Alker K, Campbell C, Figures G, Eisenhauer A, Hale S. Does tissue-type plasminogen activator have direct beneficial effects on the myocardium independent of its ability to lyse intracoronary thrombi? *Circulation*. 1989;79(5):1125-1136. http://www.ncbi.nlm.nih.gov/pubmed/2496937. Accessed November 1, 2018.

54. Kloner RA, Alker KJ. The effect of streptokinase on intramyocardial hemorrhage, infarct size, and the no-reflow phenomenon during coronary reperfusion. *Circulation*. 1984;70(3):513-521. http://www.ncbi.nlm.nih.gov/pubmed/6744555. Accessed November 1, 2018.

55. Hale SL, Kloner RA. Dabigatran treatment: effects on infarct size and the no-reflow phenomenon in a model of acute myocardial ischemia/reperfusion. *J Thromb Thrombolysis*. 2015;39(1):50-54. doi:10.1007/s11239-014-1098-x.

56. Rezkalla SH, Stankowski RV, Hanna J, Kloner RA. Management of no-reflow phenomenon in the catheterization laboratory. *JACC Cardiovasc Interv*. 2017;10(3):215-223. doi:10.1016/J.JCIN.2016.11.059.

57. Kaul S, Villanueva FS. Is the determination of myocardial perfusion necessary to evaluate the success of reperfusion when the infarct-related artery is open? *Circulation*. 1992;85(5): 1942-1944. http://www.ncbi.nlm.nih.gov/pubmed/1572050. Accessed November 1, 2018.

58. Kaul S. The "no reflow" phenomenon following acute myocardial infarction: mechanisms and treatment options. *J Cardiol*. 2014; 64(2):77-85. doi:10.1016/J.JJCC.2014.03.008.

59. Villanueva FS, Camarano G, Ismail S, Goodman NC, Sklenar J, Kaul S. Coronary reserve abnormalities in the infarcted myocardium. Assessment of myocardial viability immediately versus late after reflow by contrast echocardiography. *Circulation*. 1996; 94(4):748-754. http://www.ncbi.nlm.nih.gov/pubmed/8772698. Accessed November 1, 2018.

60. Berg R, Buhari C. Treating and preventing no reflow in the cardiac catheterization laboratory. *Curr Cardiol Rev*. 2012;8(3): 209-214. doi:10.2174/157340312803217148.

61. Awadalla H, Salloum J, Moustapha A, et al. Rheolytic thrombectomy does not prevent slow-, no-reflow during percutaneous coronary intervention in acute myocardial infarction. *Int J Angiol*. 2003;12(3):183-187. doi:10.1007/s00547-003-1005-3.

62. Mongeon F-P, Belisle P, Joseph L, Eisenberg MJ, Rinfret S. Adjunctive thrombectomy for acute myocardial infarction: a bayesian meta-analysis. *Circ Cardiovasc Interv*. 2010;3(1):6-16. doi:10.1161/CIRCINTERVENTIONS.109.904037.

63. Mancini JG, Filion KB, Windle SB, Habib B, Eisenberg MJ. Meta-analysis of the long-term effect of routine aspiration thrombectomy in patients undergoing primary percutaneous coronary intervention. *Am J Cardiol*. 2016;118(1):23-31. doi:10.1016/j.amjcard.2016.04.008.

64. Stone GW, Maehara A, Witzenbichler B, et al. Intracoronary abciximab and aspiration thrombectomy in patients with large anterior myocardial infarction. *JAMA*. 2012;307(17):1817. doi:10.1001/jama.2012.421.

65. Antoniucci D, Rodriguez A, Hempel A, et al. A randomized trial comparing primary infarct artery stenting with or without abciximab in acute myocardial infarction. *J Am Coll Cardiol*. 2003;42(11):1879-1885. http://www.ncbi.nlm.nih.gov/pubmed/14662245. Accessed November 1, 2018.

66. Neumann FJ, Kastrati A, Schmitt C, et al. Effect of glycoprotein IIb/IIIa receptor blockade with abciximab on clinical and angiographic restenosis rate after the placement of coronary stents following acute myocardial infarction. *J Am Coll Cardiol*. 2000;35(4):915-921. http://www.ncbi.nlm.nih.gov/pubmed/10732888. Accessed November 1, 2018.

67. Stone GW, Grines CL, Cox DA, et al; Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) Investigators. Comparison of angioplasty with stenting, with or without abciximab, in acute myocardial infarction. *N Engl J Med*. 2002;346(13):957-966. doi:10.1056/NEJMoa013404.