Reperfusion Strategies in Acute Coronary Syndromes

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Abstract: **The appropriate timing of angiography to facilitate revascularization is essential to optimize outcomes in patents with ST-segment–elevation myocardial infarction and non–ST-segment–elevation acute coronary syndromes. Timely reperfusion of the infarct-related coronary artery in ST-segment–elevation myocardial infarction both with fibrinolysis or percutaneous coronary intervention minimizes myocardial damage, reduces infarct size, and decreases morbidity and mortality. Primary percutaneous coronary intervention is the preferred reperfusion method if it can be performed in a timely manner. Strategies to reduce health system–related delays in reperfusion include regionalization of ST-segment–elevation myocardial infarction care, performing prehospital ECGs, prehospital activation of the catheterization laboratory, bypassing geographically closer nonpercutaneous coronary intervention–capable hospitals, bypassing the percutaneous coronary intervention–capable hospital emergency department, and early and consistent availability of the catheterization laboratory team. With implementation of such strategies, there has been significant improvement in process measures, including door-to-balloon time. However, despite reductions in door-to-balloon times, there has been little change during the past several years in in-hospital mortality, suggesting additional factors including patient-related delays, optimization of tissue-level perfusion, and cardioprotection must be addressed to improve patient outcomes further. Early angiography followed by revascularization when appropriate also reduces rates of death, MI, and recurrent ischemia in patients with non–ST-segment–elevation acute coronary syndromes, with the greatest benefits realized in the highest risk patients. Among patients with non–ST-segment–elevation acute coronary syndromes with multivessel disease, choice of revascularization modality should be made as in stable coronary artery disease, with a goal of complete ischemic revascularization. (*Circ Res*. 2014;114:1918-1928.)**

Key Words: fibrinolysis ■ myocardial infarction ■ percutaneous coronary intervention ■ reperfusion

The annual incidence of new and recurrent myocardial infarction (MI) in the United States is estimated at 720 000, with ST-segment–elevation MI (STEMI) comprising ≈29% to 47% of the events.[1] In most cases, MI occurs because of rupture or fissuring of an inflamed thin-capped fibroatheroma containing a lipid-rich necrotic core with superimposed

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Nonstandard Abbreviations and Acronyms

ACCF	American College of Cardiology Foundation
AHA	American Heart Association
D2B	door-to-balloon
ED	emergency department
FMC	first medical contact
MI	myocardial infarction
NSTEACS	non–ST-segment–elevation acute coronary syndrome
STEMI	ST-segment–elevation MI
TIMI	thrombolysis in myocardial infarction

secondary thrombosis causing reduced blood flow and myocardial cell death. A completely occlusive thrombus typically presents as STEMI, whereas non–ST-segment–elevation acute coronary syndromes (NSTEACS) result often from a partially occlusive thrombus, often associated with microthrombi that detach and embolize downstream.

Although cardiovascular disease remains the most common cause of mortality in the United States, the case fatality rate of MI has fallen dramatically in the past 3 decades, in part because of the widespread use of reperfusion therapy.[2] Effective and timely reperfusion of the infarct-related coronary artery is central to optimal treatment for both STEMI[3–5] and NSTEACS.[6] In STEMI, compared with fibrinolysis, primary percutaneous coronary intervention (PCI) establishes more consistent and predictable epicardial artery recanalization, significantly lowers the risk of intracranial hemorrhage and stroke, reduces recurrent ischemia and reinfarction, and improves survival.[7,8] Early angiography followed by revascularization when appropriate also improves clinical outcomes in patients with NSTEACS, with the greatest benefits realized in the highest risk patients.[6] Because epicardial artery reperfusion does not guarantee myocardial perfusion, strategies for cardioprotection and optimization of tissue-level reperfusion are also essential (Figure 1). The goal of this article is to highlight reperfusion strategies to achieve faster and more effective epicardial vessel and microvascular reperfusion in patients with STEMI and NSTEACS, as well as temporal and logistic factors that may affect treatment outcomes and thus clinical decision making.

Reperfusion in STEMI

Ischemic Time, Myocardial Necrosis, and Mortality

The amount of myonecrosis per unit time from the moment of coronary occlusion is curvilinear, with the maximum amount of infarction occurring in the first few hours.[9] Several clinical studies have confirmed the important relationship between achieving prompt antegrade coronary flow of the infarct artery and improved clinical outcomes for both primary PCI and fibrinolysis. An analysis of 50 246 patients from 22 trials by Boersma et al[10] of treatment effect of fibrinolysis versus control in randomized trials suggested that the 35-day mortality benefit associated with early treatment equated to 1.6 lives per 1000 patients per hour of delay from symptom onset to treatment, with even more of an effect of time in the early hours (Figure 2). De Luca et al[11] demonstrated in an observational study of 1791 patients that after adjustment for age, sex, diabetes mellitus, and previous revascularization, each 30-minute delay in primary angioplasty for STEMI was associated with a relative risk of 1.075 for 1-year mortality. McNamara et al[12] in a study of 29 222 patients from the National Registry of Myocardial Infarction reported a 1.42 odds ratio for increased mortality in patients for whom the door-to-balloon (D2B) time was >90 compared with <90 minutes. From 1994 to 2006 in National Registry of Myocardial Infarction, the median D2B time was reduced year over year in the United States from 120 to 87 minutes, which was accompanied by a steady decrease in in-hospital mortality from 8.3% to 6.6%.[13]

Given this association between shorter time to reperfusion and survival,[11,14] D2B time became the focus of regional[15] and national[16,17] quality improvement initiatives. The D2B Alliance[17] and Mission: Lifeline[16] campaigns were launched to guide adoption of proven strategies to reduce reperfusion delays and improve systems of STEMI care. Several strategies were developed, tested, and formally incorporated into clinical guidelines to shorten D2B times.[18,19] With concerted efforts using such evidence-based strategies, there have been significant improvements in D2B times across the country and across different types of hospitals.[20–22] However, in a more recent analysis from the National Cardiovascular Data Registry of 96 738 primary PCI procedures performed between July 2005 and June 2009, Menees et al[21] showed that despite continuing reductions in national D2B times (from median 83 to 67 minutes), in-hospital mortality rates have remained unchanged, although adjustment for change in cardiac arrest was not possible. Possible explanations include reductions in D2B time that are too small to reduce infarct size or initiation of treatment that is too late or follow-up that is too short to show improvement in survival.[23] D2B time is only one component of total ischemic time, and because D2B time is reduced, delays to hospital presentation become a relatively larger fraction of reperfusion delay. This observation also emphasizes that other components of the reperfusion process must be improved (eg, more effective myocardial reperfusion, reduction in reperfusion injury) to enhance outcomes in STEMI further.

Selecting a Reperfusion Method

The total ischemic time is of paramount importance regardless of whether reperfusion is achieved with fibrinolysis or PCI.[18] Selecting the optimal reperfusion strategy requires customization based on patient factors including time from symptom onset to first medical contact (FMC), the amount of myocardium at risk, the presence of shock or severe heart failure, the risk of bleeding with fibrinolysis, and the time required to perform PCI (including transfer to a PCI-capable hospital; Figure 3). In 2003, in a meta-analysis of 7739 patients enrolled collectively in 23 randomized trials, Keeley et al[7] demonstrated reduced rates of reinfarction, hemorrhagic stroke, and mortality with primary PCI compared with fibrinolytic therapy (8% versus 14%; $P<0.001$). In the same year, a meta-analysis of trials comparing transferring patients with STEMI for primary PCI to immediate fibrinolysis at the non–PCI-capable hospital followed by transfer and PCI demonstrated reductions in death, MI, and stroke in patients in whom fibrinolysis was withheld (7.8% versus 13.5%; $P<0.001$).[24] Thus, both the American College of Cardiology Foundation (ACCF)/American Heart

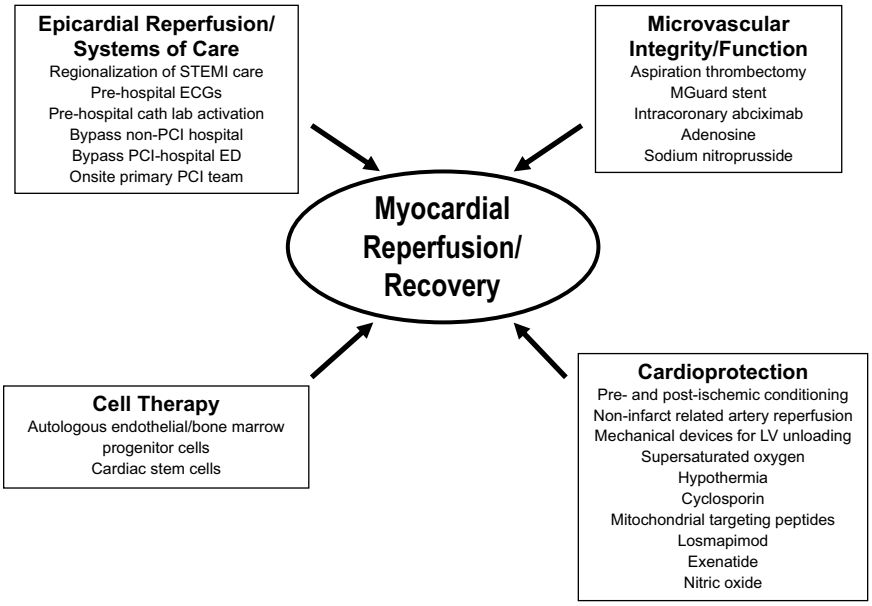

Figure 1. Targets for myocardial perfusion. Multifaceted approach to optimize epicardial artery and tissue-level myocardial perfusion. ED indicates emergency department; LV, left ventricular; PCI, percutaneous coronary intervention; and STEMI, ST-segment–elevation myocardial infarction.

Association (AHA) and the European Society of Cardiology STEMI guidelines recommend primary PCI as the preferred reperfusion strategy to fibrinolysis, provided it can be delivered by experienced operators in a timely fashion within 90 minutes of FMC.[25,26] A more contemporary meta-analysis of 5741 patients with STEMI in 11 randomized trials compared transfer for primary PCI to fibrinolysis performed at the non–PCI-capable hospital and demonstrated that primary PCI provided a significant reduction in mortality (5.6% versus 6.8%; P=0.02), reinfarction (2.1% versus 4.7%; P<0.0001), and stroke (0.7% versus 1.7%; P=0.0005) at 30 days.[27]

Despite these results, the acceptable delay between the time when fibrinolysis could be given (door-to-needle time) and time when reperfusion with primary PCI could be achieved (D2B time) has been the subject of great debate, and local geographical considerations have often determined which reperfusion strategy is adopted. The DANAMI-2 (Danish multicentre randomized study of fibrinolytic therapy vs. primary angioplasty in acute myocardial infarction) study showed that despite an average first door-to-device time delay of ≈110 minutes, a reperfusion strategy involving the transfer of patients with STEMI from a non–PCI-capable hospital to a PCI-capable hospital for primary PCI was superior to the use of fibrinolysis at the referring hospital, driven primarily by a reduction in reinfarction.[29] In an observational analysis of 192 509 patients from National Registry of Myocardial Infarction, Pinto et al[30] demonstrated that primary PCI is associated with lower mortality when the mean PCI-related delay is <114 minutes, but with large variability, depending on patient factors such as symptom duration, age, and infarct location. Pinto et al[31] subsequently reported from a propensity-matched observational analysis of >19 000 patients with STEMI that the mortality advantage of primary PCI compared with fibrinolysis seemed to be lost when PCI-related delay exceeded 121 minutes. Based on these data, the latest ACCF/AHA guidelines for STEMI[18] extended the acceptable door-to-device time to 120 minutes for patients presenting to non–PCI-capable hospitals but with a continued goal of 90 minutes, an adjustment consistent with current European guidelines.[26] A new metric for non–PCI-capable hospitals transferring patients to PCI-capable hospitals is the door-in-door-out time, which should be <30 minutes.[32] Fibrinolytic therapy, in the absence of contraindications to its use, should in general be administered within 30 minutes of hospital arrival in patients with STEMI at non–PCI capable hospitals when the anticipated FMC-to-device time at a PCI-capable hospital is >120 minutes. Despite evidence for safety and feasibility of prehospital fibrinolytic therapy,[33] unlike some regions in Europe, fibrinolytic therapy is rarely used in the prehospital setting in the United States. Rural areas where prehospital fibrinolysis would potentially be of most benefit neither have the resources to train paramedics nor the funding for necessary equipment.

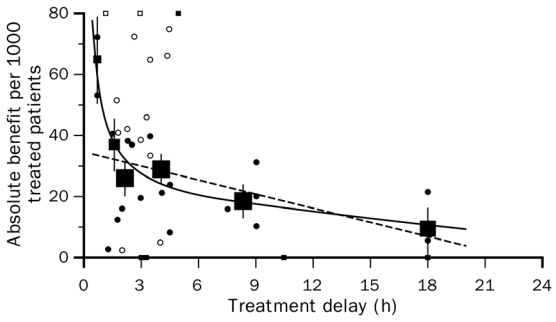

Figure 2. Mortality reduction as a function of treatment delay. Small closed and open dots represent information from trials; small squares represent data beyond scale of x/y cross. The linear ($34.7–1.6x$) and nonlinear ($19.4–0.6x+29.3x^{-1}$) regression lines are fitted within these data, weighted by inverse of the variance of the absolute benefit in each data point. Black squares represent average effects in 6 time-to-treatment groups (areas of squares inversely proportional to variance of absolute benefit described). Reproduced from Boersma et al[10] with permission of the publisher. Copyright ©1996, Elsevier.

The routine early use of angiography after fibrinolysis with the intent to perform PCI, referred to as a pharmacoinvasive strategy, has been investigated in several clinical trials against the previously standard approach of reserving early angiography for failed fibrinolysis or hemodynamic instability.

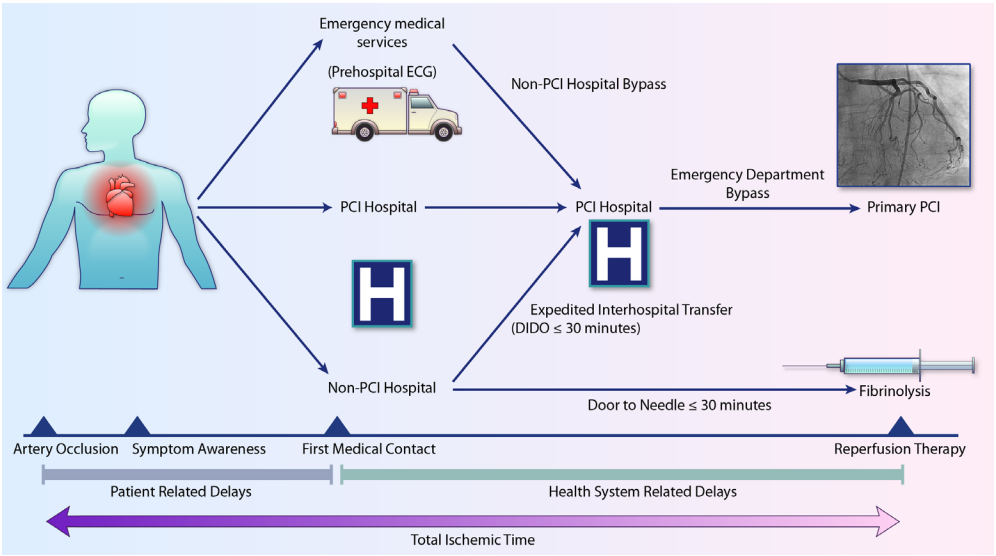

Figure 3. Patient-related and health system–related delays in ST-segment–elevation myocardial infarction. DIDO indicates door-in-door-out; and PCI, percutaneous coronary intervention. Adapted from Windecker et al[28] with permission of the publisher. (Illustration Credit: Ben Smith.)

The TRANSFER-AMI (Trial of Routine Angioplasty and Stenting After Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction) study was the largest (n=1059) of the randomized controlled trials evaluating transfer for coronary angiography and revascularization among high-risk patients and showed a significant reduction in the combined primary end point of death, recurrent MI, recurrent ischemia, new or worsening heart failure, or shock at 30 days with immediate transfer for angiography compared with conservative care.[34] In a meta-analysis that included 7 randomized controlled trials of early transfer for catheterization, a strategy of routine early catheterization after fibrinolysis was associated with a significant reduction in the incidence of death or MI at 6 to 12 months, without an increase in major bleeding.[35]

In the STREAM (Strategic Reperfusion Early After Myocardial Infarction) trial, a pharmacoinvasive strategy with prehospital or early fibrinolysis coupled with coronary angiography within 6 to 24 hours of randomization in stable patients was compared with urgent transfer for primary PCI in 1892 patients with STEMI who presented within 3 hours after symptom onset and were unable to undergo primary PCI within 60 minutes of FMC.[36] In this trial, there was a similar rate of the primary end point of death, shock, congestive heart failure, or reinfarction at 30 days between the 2 strategies (12.4% versus 14.3%, respectively; P=0.21). Intracranial hemorrhage occurred more frequently in the pharmacoinvasive group than with primary PCI (0.96% versus 0.21%; P=0.04). The increase in intracranial hemorrhage events in the pharmacoinvasive group was greatest among patients aged ≥75 years, which led to a 50% reduction in body weight–based dose of tenecteplase in these individuals, with an acceptable subsequent safety profile. These results support withholding fibrinolysis for preferential transfer for primary PCI in all patients except those in whom large PCI-related delays are anticipated.[37] These results are also in accordance with practice guidelines and provide support for the use of fibrinolytic therapy with routine early transfer to a PCI-capable hospital when a delay of >2 hours is anticipated from FMC-to-device activation in patients presenting early after symptom onset, especially in younger patients. Transfer to a PCI center after fibrinolysis is indicated for patients with cardiogenic shock and heart failure (class I) and is reasonable for patients with failed reperfusion requiring rescue and also for patients with successful reperfusion for early angiography, ideally within 24 hours (class IIa).[18]

Strategies to Shorten Time to Reperfusion

Delays in reperfusion can arise between symptom onset and FMC (patient related) and between FMC and reperfusion treatment (health system related).

Reducing Patient-Related Delays

Patients with STEMI do not seek medical care for ≈1.5 to 2 hours after symptom onset, and there has been little change in this interval during the past 10 years.[38,39] Patient delays are longer in women, blacks, Medicaid-only recipients, and especially the elderly.[40,41] Such delays may be avoided by making anticipatory plans for timely recognition and response to an acute event. The AHA and National Institutes of Health Act in Time to Heart Attack Signs campaign stresses that patients can increase their chance of surviving STEMI by learning warning symptoms, filling out a survival plan, and discussing risk reduction with their physician. Several studies have also demonstrated a significant association between arrival to hospital by ambulance and earlier delivery of reperfusion therapy.[42,43] Approximately 1/300 patients with chest pain transported to emergency departments (EDs) by private vehicles experience cardiac arrest en route.[44] Thus, patients with ischemic symptoms should be instructed to call 911 rather than transport themselves to hospital by friends or relatives.

Reducing Health System–Related Delays

Regionalization of STEMI Care

Efficient reperfusion in STEMI requires multidisciplinary coordination between the various points of medical care. These

considerations fueled the evolution of systems and centers of care for patients with STEMI. In 2007, the AHA launched Mission: Lifeline, a community-based initiative to improve STEMI systems of care; and in 2009, the ACCF/AHA supported this approach with a class I recommendation,[45] consistent with the European guidelines.[46] Implementation of STEMI care systems has been associated with significant improvement in overall use and timeliness of reperfusion.[47,48] A PCI-based strategy implemented through a comprehensive systems approach has thus far been associated with reduced mortality outside[49,50] but not within the United States.[15] The ongoing regional systems of care demonstration project: Mission: Lifeline STEMI Systems Accelerator project designed in collaboration with the AHA to implement STEMI care systems in 17 major metropolitan regions encompassing >1500 emergency medical service agencies and 450 US hospitals will provide further data on the effect of regionalization of STEMI care on patient outcomes.[51]

Prehospital ECG and Catheterization Laboratory Activation

In a report from the National Cardiovascular Data Registry, only one quarter of patients with STEMI transported by emergency medical service received a prehospital ECG, with use of a prehospital ECG associated with accelerated diagnosis and activation of the PCI-capable center, greater use of reperfusion therapy, faster reperfusion times, and a trend toward lower mortality.[52] Field activation of the catheterization laboratory while the patient is en route to the hospital has been associated with 14 to 43 minute shorter reperfusion times compared with waiting for hospital arrival before catheterization laboratory activation, with the greatest benefits during off-hours and for patients with long transport times.[19,53–56] Although paramedics can reliably interpret STEMI on prehospital ECGs and this is the most common means of field diagnosis of STEMI,[57,58] uptake of catheterization laboratory activation by paramedics has been impeded in some regions by concerns about high false activation rates. With enhanced paramedic training and use of computerized programs for ECG interpretation, similar catheterization laboratory activation cancellation rates have been demonstrated for paramedic and ED physicians.[59,60]

Bypassing Non–PCI-Capable Hospitals

Major delays still exist for patients who are transferred by emergency medical service from a non–PCI-capable hospital to a PCI-capable facility. Only 11% of such patients have door-in-door-out times less than the recommended 30 minutes,[32] and only 13% of transferred patients are treated with PCI within 90 minutes of arrival at the first hospital.[15] Bypassing geographically closer hospitals without primary PCI capabilities has been associated with faster reperfusion times and ≈3-fold greater likelihood of achieving target guideline of <90 minutes from FMC to PCI.[61] This strategy has been implemented successfully in other countries[62,63] and has been proposed as one means of achieving more rapid reperfusion in STEMI.[64]

Bypassing PCI-Capable Hospital ED

To optimize timely reperfusion, the 2012 European Society of Cardiology STEMI guidelines recommend bypassing the PCI-capable hospital ED by transporting patients identified with STEMI on a prehospital ECG directly from the field to the cardiac catheterization laboratory.[46] However, the updated ACCF/AHA STEMI guidelines have not yet promoted this strategy.[18] Multiple, unrelated emergency medical service providers, absence of ambulance physician staffing, and lack of information technology to support consistent digital ECG transmission have limited implementation and broad experience with this strategy in the United States, representing an opportunity for future improvement. In this regard, bypass of the PCI hospital ED in the United States has been associated with ≈20 minute faster reperfusion and ≈50% greater likelihood of achieving target guideline of <90 minutes from FMC to PCI and a tendency for lower mortality.[65,66]

Strategies for Cardioprotection and Optimization of Tissue-Level Perfusion

Cardioprotection refers to interventions beyond simple reperfusion therapy to enhance myocardial salvage and left ventricular function.

Protection From Distal Embolization

Plaque material and thrombi can block the distal vasculature, and endothelial dysfunction, leukocyte plugs, and external compression resulting from interstitial edema and cardiac myocyte contraction, as well as extensive myonecrosis with capillary destruction, can compromise the microcirculation. These processes may cause inadequate myocardial perfusion, despite coronary artery patency. Thrombus embolization is thought to be ubiquitous during primary PCI, and whether simple mechanical aspiration before PCI improves clinical outcomes has been a matter of great debate for nearly a decade. In the TAPAS (Thrombus Aspiration during Percuntaneous coronary intervention in Acute myocardial infarction Study) trial of 1071 patients with STEMI undergoing primary PCI, manual aspiration thrombectomy was associated with improved parameters of reperfusion and long-term outcomes including mortality.[67,68] However, 2 recent trials have failed to show benefits of routine manual aspiration thrombectomy. In the INFUSE-AMI (Intracoronary Abciximab and Aspiration Thrombectomy in Patients with Large Anterior Myocardial Infarction) trial, 30-day infarct size was similar among 452 patients with large anterior STEMI treated with and without aspiration thrombectomy.[69] In the TASTE (Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia) trial, the primary end point of 30-day mortality was similar in 7244 randomized patients undergoing primary PCI treated with and without aspiration thrombectomy (2.8% versus 3.0%; P=0.63).[70] The ongoing TOTAL (Trial of Routine Aspiration Thrombectomy With Percutaneous Coronary Intervention (PCI) Versus PCI Alone in Patients with ST-Segment Elevation Myocardial Infarction Undergoing Primary PCI) trial (NCT01149044) will provide additional insights on the role of routine aspiration thrombectomy during primary PCI.

Compared with bare metal stents, first-generation drug-eluting stents reduce recurrent ischemia and repeat revascularization, with no improvement in reinfarction or mortality. However, this benefit was offset in some patients by increase in late stent thrombosis.[71] In the EXAMINATION (Everolimus-Eluting Stents Versus Bare-Metal Stents in

ST-Segment Elevation Myocardial Infarction) trial, among 1504 randomized patients with STEMI, a newer-generation everolimus-eluting stent with a cobalt–chromium platform, thinner struts, and thromboresistant fluoropolymer resulted in fewer stent thromboses and target lesion revascularizations than a comparable bare metal stent.[72] The MGuard Prime Stent system, a cobalt chromium balloon-expandable metallic stent wrapped with an expandable polyethylene theraphthalate polymer mesh, has been developed to trap atherothrombotic debris between the mesh and artery wall, thus preventing distal embolization. Compared with conventional stents, the MGuard demonstrated superior rates of epicardial coronary flow and complete ST-resolution in the 433 patient MASTER (MGUARD for Acute ST Elevation Reperfusion) randomized trial.[73] The larger MASTER II trial (NCT01869738), designed to evaluate the effects of the MGuard on infarct size and clinical outcomes, is currently enrolling patients. A novel self-expanding stent designed to reduce strut malapposition is also under investigation in STEMI.[74]

There are conflicting reports on the effect of intracoronary abciximab on infarct size and clinical outcomes.[75–77] This is, in part, because of differences in patient selection, devices, and study methodology. In the INFUSE-AMI study, abciximab was delivered locally at the site of the infarct lesion via the ClearWay RX infusion catheter, a microporous weeping polytetrafluoroethylene balloon catheter (Atrium Medical) in patients with large anterior STEMI undergoing primary PCI. Intralesional abciximab administration resulted in a significant but modest reduction in infarct size at 30 days, without improved indices of myocardial reperfusion, ST-segment resolution, or early clinical outcomes.[69] Larger trials are required to determine whether the degree of early infarct size reduction achieved with intralesional abciximab in this study translates into improved clinical outcomes.

Ischemic Postconditioning and Remote Ischemic Preconditioning

Reperfusion is accompanied by striking changes in oxygen tension, pH, and intracellular distribution of Ca^{2+} and Na^{+}, which can induce cardiomyocyte death, a phenomena termed ischemia reperfusion injury. It has been suggested that ischemia reperfusion injury may account for 40% to 50% of final MI size, thus mitigating the full benefits of reperfusion.[78] Endogenous cardioprotective strategies, namely ischemic postconditioning, performed after stenting of the infarct-related artery by cycles of low-pressure balloon inflation upstream of the stent has been associated with reduction in infarct size in some[79–81] but not all studies.[82] The ongoing DANAMI-3 trial (NCT01435408) investigating the effects of ischemic postconditioning on clinical outcomes in primary PCI-treated patients with STEMI will offer additional insights. The ischemic conditioning stimulus can also be applied to an organ or tissue remote from the heart either before or after reperfusion. In small randomized studies, cycles of upper arm cuff inflation and deflation to pressures above the systolic blood pressure performed before reperfusion have been associated with lower peak troponin I levels[83] and greater myocardial salvage index by SPECT (Single-photon emission computed tomography) at 30 days.[84] In addition, in a randomized study of 333 patients with STEMI in the CONDI (Effect of Remote Ischaemic Conditioning on Clinical Outcomes in ST-elevation Myocardial Infarction Patients Undergoing Primary Percutaneous Coronary Intervention: A Multinational Multicentre Randomised Controlled Clinical Study) trial, compared with no remote ischemic preconditioning, 4 cycles of 5-minute inflation followed by 5-minute deflation of a blood pressure cuff was associated with a lower rate of the composite of all-cause mortality, MI, readmission for heart failure, and ischemic stroke/transient ischemic attack.[85] However, these results require confirmation in a larger multicenter trial (eg, CONDI2, NCT 01857414) before remote ischemic conditioning can be implemented in routine practice as an adjunct to primary PCI.

Percutaneous Mechanical Circulatory Support

Intra-aortic balloon counterpulsation augments coronary blood flow,[86] unloads the left ventricle, and reduces myocardial oxygen demand.[87] Although these favorable hemodynamic effects have demonstrated improvements in outcomes among patients with acute MI complicated by cardiogenic shock in some,[88] but not all studies,[89] early planned intra-aortic balloon counterpulsation use did not reduce myocardial infarct size measured by cardiac MRI among patients with anterior STEMI without cardiogenic shock.[90] Compared with intra-aortic balloon counterpulsation, Impella LP 2.5 may provide superior hemodynamic support and serve as a more effective bridge to recovery or transplantation, although experience in this setting is limited and further studies are needed.[91]

Revascularization of Noninfarct Stenosis During Primary PCI

Multivessel disease is seen in up to 60% of patients presenting with STEMI and portends a worse prognosis compared with patients with STEMI with single-vessel disease.[92,93] The current ACCF/AHA guidelines recommend against revascularization of the noninfarct-related arteries at the time of the index primary PCI procedure except in patients with hemodynamic instability.[18] A recent systematic review and meta-analysis showed that worse clinical outcomes associated with performing PCI of noninfarct-related stenosis during the index primary PCI procedure have been observed in nonrandomized cohort studies but not in the small number of randomized controlled trials.[94] More recently, the 465 patient PRAMI (Preventive Angioplasty in Myocardial Infarction Trial) study demonstrated a reduction in the primary composite of death, nonfatal MI, or refractory angina with preventative angioplasty of noninfarct-related lesions during the primary PCI procedure compared with reserving revascularization for ongoing symptoms and ischemia.[95] Additional mechanistic and larger scale definitive randomized controlled studies, some of which are ongoing (COMPLETE, NCT01740479), are required to guide optimal management of noninfarct-related stenoses after primary PCI of the infarct-related artery.

Notable Experimental Cardioprotective Strategies

Novel cardioprotective interventions are currently under investigation. These include cyclosporine A (CIRCUS,

NCT01502774; CYCLE, NCT 01650662), mitochondrial targeting peptides—bendavia[96] (EMBRACE, NCT 01572909) and TRO40303[97] (MITOCARE, NCT 01374321), supplemental oxygen (DETO2X-AMI, NCT 01787110), IK-5001, an aqueous mixture of sodium alginate and calcium gluconate (PRESERVATION 1, NCT 01226563), adenosine and sodium nitroprusside (MVO, NCT 01747174), metformin (GIPS-III, NCT 01217307), exenatide (EMPRES, NCT 01938235), losmapimod (SOLSTICE, NCT00402363),[98] and nitric oxide (NOMI, NCT 01398384).

Revascularization for NSTEACS

Routine Invasive Versus Selective Invasive Approach

Many randomized controlled trials and meta-analyses have compared a routine invasive strategy (catheterization followed by revascularization with PCI or coronary artery bypass grafting [CABG] when appropriate) with a selective invasive approach (routine catheterization deferred unless recurrent spontaneous or provoked ischemia) in patients with NSTEACS. In a meta-analysis based on individual patient data from 5467 patients in 3 contemporary randomized trials, a routine invasive strategy was associated with an overall reduction in rates of death and nonfatal MI at 5 years compared with a selective invasive strategy.[6] The benefit of a routine invasive approach was most pronounced in high-risk patients (11.1% absolute risk reduction; number needed to treat to prevent 1 cardiovascular death or MI=9), whereas the absolute reduction in the intermediate and low-risk groups was 3.8% and 2.0%, respectively (numbers needed to treat=26 and 50). This relationship between risk score and absolute benefit from an invasive strategy was also demonstrated in the earlier TACTICS-TIMI 18 (Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy - Thrombolysis in Myocardial Infarction 18) trial.[99] Among patients at low risk (thrombolysis in myocardial infarction [TIMI] score 0–2), there was no difference in the primary end point of death, MI, and rehospitalization for acute coronary syndrome (ACS) at 6 months between the routine invasive and conservative approaches; conversely, there was a significant reduction in the primary end point with an invasive approach among patients at intermediate risk (TIMI score 3–4) and particularly in those at high risk (TIMI score 5–7).

Timing of Angiography and Intervention

In patients with NSTEACS in whom an invasive approach is planned, the optimal timing of catheterization and revascularization has also been extensively evaluated. In the TIMACS (Timing of Intervention in Acute Coronary Syndrome) trial of 3030 patients with NSTEACS, patients undergoing early catheterization (within 24 hours after randomization) compared with delayed catheterization (≥36 hours after randomization, median time 50 hours) did not have a significant difference in the primary composite of death, MI, or stroke at 6 months (hazard ratio, 0.85; 95% confidence interval, 0.68–1.06; P=0.15).[100] The primary end point was reduced with early intervention, however, in the third of patients who were at highest risk (Global Registry of Acute Coronary Events score ≥141; hazard ratio, 0.65; 95% confidence interval, 0.48–0.89; P interaction=0.01). In addition, early intervention did reduce the 6-month risk of refractory ischemia in the entire group by 70%. In the ISAR-COOL (Intracoronary Stenting with Antithrombotic Regimen Cooling Off) trial,[101] 410 intermediate-to-high risk patients with NSTEACS with either ST-segment depression or elevated troponin were randomly assigned to a early versus delayed invasive strategy (median time to catheterization 2.4 versus 86 hours). The early invasive strategy compared with the delayed invasive strategy was associated with a reduction in death or large MI at 30 days because of fewer precatheterization events. In the ABOARD (Acute Coronary Syndromes Randomized for an Immediate or Delayed Intervention) trial of 352 intermediate-high risk (TIMI score ≥3) patients with NSTEACS, there was no difference in the primary outcome of peak troponin I levels or secondary outcomes of death, MI, or urgent revascularization at 1 month between immediate (median 70 minutes after randomization) versus next working day (median 21 hours after randomization) angiography and revascularization.[102]

Of note, all of these studies excluded patients at high risk, that is, with refractory angina, severe heart failure, life-threatening ventricular arrhythmias, or hemodynamic instability, in whom most agree urgent catheterization and revascularization are indicated. Thus, a routine invasive approach within 24 hours is recommended for high-risk patients with NSTEACS (eg, recurrent angina or ischemia at rest or with low-level activities, despite intensive medical therapy, elevated troponin, new ST-depression). For patients at low risk (eg, low TIMI [0–2] or Global Registry of Acute Coronary Events [≤108] risk score), the ACCF/AHA guidelines allow for either a conservative or delayed invasive approach,[103] whereas the European Society of Cardiology guidelines recommend against a routine initial invasive approach.[104] Thus, systematic risk stratification with use of risk assessment tools is critical in the selection and timing of a treatment strategy in NSTEACS.

Culprit Only Versus Complete Revascularization

Multivessel disease is also frequent in NSTEACS and portends a worse prognosis compared with single-vessel disease. The strategy of multivessel revascularization for suitable significant stenosis rather than stenting the culprit lesion only has not been evaluated in a randomized fashion. In a single-center observation study of 1240 patients with NSTEACS and multivessel disease, multivessel intervention was associated with lower rates of death, MI, or revascularization after adjusting for baseline and angiographic characteristics compared with culprit-only stenting.[105] In a single-institution study of 1100 consecutive patients with NSTEACS with multivessel disease, multivessel revascularization was associated with lower repeat revascularization, with no difference in rates of death or MI.[106] In the largest study of 105 866 multivessel patients with coronary artery disease with NSTEACS from the National Cardiovascular Data Registry, compared with single-vessel PCI, multivessel PCI was associated with lower procedural success but similar in-hospital mortality, bleeding, renal failure, and nonfatal cardiogenic shock.[107] Based on the available nonrandomized observational data, multivessel revascularization seems reasonable in patients with NSTEACS with low risk of morbidity, high likelihood of success, and moderate to large area of ischemic myocardium.

Choice of Revascularization Strategy

The choice of modality for multivessel revascularization—CABG versus multivessel PCI—has also not been studied in a randomized fashion exclusively in patients with NSTEACS. In a propensity-matched analysis of 5627 patients with NSTEACS with multivessel disease from the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial, PCI-treated patients had lower rates of stroke, MI, bleeding, and renal injury, with similar 1-month and 1-year mortality, but significantly higher rates of unplanned revascularization.[108] These results are consistent with the SYNTAX (Synergy Between PCI with TAXUS and Cardiac Surgery) trial, in which 28.5% of 1800 patients randomized to PCI versus CABG had a recent ACS.[109] Among 1900 patients with diabetes mellitus in the FREEDOM (Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease) trial, of which ≈30% had recent ACS, CABG was associated with lower 5-year rate of both death from any cause and MI, with higher rate of stroke.[110] However, subanalyses from these trials have not been reported.

Calculation of Society of Thoracic Surgery and SYNTAX scores is reasonable, and a Heart Team approach to revascularization decisions is recommended in patients with NSTEACS and unprotected left main or complex coronary artery disease. In patients stabilized after an episode of ACS, the choice of revascularization modality is made as in stable coronary artery disease. In addition to angiographic complexity and suitability, clinical factors that may influence choice of revascularization include patient comorbidities including diabetes mellitus and renal dysfunction, prior CABG, left ventricular systolic dysfunction, and ability to comply with dual antiplatelet therapy.[111]

Conclusions

Quality improvement efforts during the past decade on the local, regional, and national levels have successfully translated into faster reperfusion times in patients with STEMI, which have been associated with substantial survival benefits. However, in-hospital mortality rates during the past several years have changed little, despite further reductions in D2B times, suggesting that additional factors must be addressed to improve patient outcomes further. Individual and population-based efforts are required to increase patient and public awareness of symptoms and the importance of earlier presentation. Continued efforts and resources are required to implement regional systems for STEMI care and use proven strategies associated with faster reperfusion including prehospital ECGs, prehospital catheterization laboratory activation, bypassing non–PCI capable hospitals, and bypassing PCI hospital EDs. In addition to expediting epicardial artery recanalization, additional studies are required to explore strategies to improve microvascular and tissue-level perfusion and protect the myocardium from reperfusion injury. Finally, most patients with NSTEACS benefit from a strategy of early angiography followed by revascularization when appropriate, with the greatest benefits realized in the highest risk patients. The choice of modality for multivessel revascularization specifically in patients with NSTEACS has also not been studied in a randomized fashion, and thus, among patients stabilized after an episode of ACS, the choice of revascularization modality should be made as in stable coronary artery disease, with a goal of complete ischemic revascularization.

Disclosures

Dr Dangas is a consultant to Medtronic and his spouse is on the Advisory board to Abbott Vascular and Boston Scientific. Dr Stone is Consultant to Boston Scientific, Atrium, InspireMD, Eli Lilly, and Daiichi Sankyo. Dr Granger had a research contracts from AstraZeneca, GSK, Merck, Sanofi-Aventis, BMS, Pfizer, Bayer, Diaichi Sankyo, The Medicines Company, Medtronic Foundation, and Boehringer Ingelheim, and he receives consulting/honoraria from AstraZeneca, GSK, BMS, Pfizer, Lilly, Novartis, Roche, Boehringer Ingelheim, Janssen, The Medicines Company, and Sanofi-Aventis; for full listing, see www.dcri.duke.edu/research/coi.jsp. The other author reports no conflicts.

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