

CardiologyRounds™

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OF BRIGHAM AND WOMEN'S HOSPITAL, BOSTON, MASSACHUSETTS

Non-reperfusion therapies for ST elevation MI patients who present late or are ineligible for reperfusion

MARC COHEN, MD, FACC

In the setting of acute ST segment elevation myocardial infarction (STEMI), myocardial necrosis begins within minutes, and is largely complete within a few hours. The primary objectives of intervention involve recanalization of the infarct-related artery (IRA) as rapidly as possible, and prevention of its reocclusion.¹ This has been pursued pharmacologically with thrombolysis and manipulation of the thrombotic cascade, or mechanically with percutaneous coronary intervention (PCI) and/or coronary bypass surgery. Timely intervention reduces the ultimate size of the infarction, leading to greater preservation of ventricular function and presumably, improvements in survival.¹ Angiographic data from the GUSTO I study² offered support for this contention, since early patency of the IRA was associated with improved outcome. The treatment algorithm that evolved is presented in Figure 1. However, not every STEMI patient is suitable for reperfusion, nor does every eligible patient receive it. The goal of this issue of *Cardiology Rounds* is to explore the best management of STEMI patients who are not reperfused, for whatever reason.

Reperfusion – current trends

The records of 1,514,292 patients enrolled in the National Registry of Myocardial Infarction (NRFMI) reveal several important trends during the 1990s.³ Apart from showing that both the average age and weight of STEMI patients are rising, these US data illustrate two major issues:

- reperfusion remains under-utilized, and
- the eligibility of the patient pool for reperfusion may be changing.

The proportion of all STEMI patients who received immediate reperfusion decreased from 37% to 28% during the 1990s.³ This decline reflects a falling proportion of “reperfusion-eligible” patients (patients with appropriate ECGs who present early enough) that decreased from 36% to 27% between 1994 and 1999. Conversely, the proportion of non-ST elevation myocardial infarction (NSTEMI) patients rose from 45% to 63% during the same period. Among those patients eligible for reperfusion, the proportion that were reperfused increased only slightly from 68.8% to 70%. Within this group, the use of thrombolysis declined, as primary PCI increased from 1994 to 1999. Still, over one-quarter of STEMI patients who appear to be eligible for reperfusion therapy do not receive it.⁴⁻¹⁰ In a major review of 84,663 STEMI patients presenting within 6 hours and without contraindications to thrombolysis, 24% of reperfusion eligible patients did not receive any form of reperfusion therapy.

The independent predictors of non-use of reperfusion therapy are older age, female gender, left bundle branch block, and absence of chest pain on presentation (Table 1). Other differences in reperfusion (both PCI and lysis) usage rates were demonstrated by Eagle et al¹¹ who studied 2,501 patients with STEMI within 12 h of symptoms followed in the GRACE Registry. They found differences in the treatment approach between teaching and non-teaching hospitals; the



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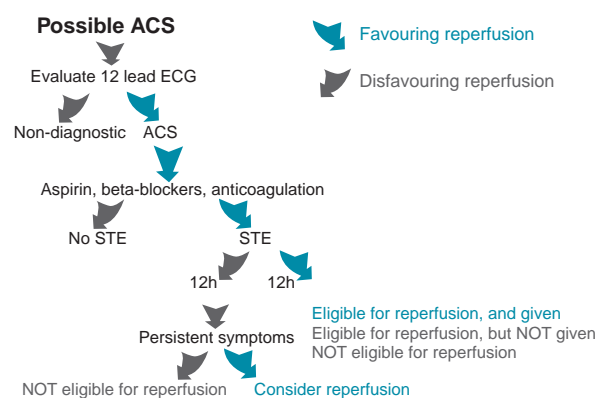
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Figure 1: The algorithm of treatment for patients presenting with STEMI



presence or absence of a cardiac catheterization laboratory; as well as geographical variations in the standard of treatment. Overall, the proportion of eligible patients receiving neither PCI, nor thrombolytic in the GRACE Registry was approximately 20%.

Under-utilization – Addressing the time window for reperfusion

Early prospective trials: Early data from ISIS 2 showed greater mortality benefit among patients who were treated sooner, but there was still significant benefit in patients reperfused 12 to 24 hours after onset of pain.⁶ The LATE study¹² randomized 5,711 patients to thrombolysis with rtPA, or placebo, starting 6 to 24 hours after onset of ischemic symptoms. The difference in survival between the two treatments was not significant. However, the subset of patients thrombolysed within 12 hours of pain onset experienced a 25% reduction in 35-day mortality (8.9% vs 11.97%, $P=0.02$).

In contrast, the EMERAS study¹³ did not provide evidence of benefit among patients receiving late thrombolysis with streptokinase, although there were non-significant trends for in-hospital mortality in favor of thrombolytics among patients treated 7 to 12 hours following onset of pain. The Western Washington study¹⁴ provided conflicting evidence about late reperfusion >5 hours. Lytic therapy was not associated with superior global or regional LV function at 2 months, compared to placebo, but successful

Table 1: Predictors of thrombolytic non-usage

Condition	OR (95% CI) of not receiving thrombolysis
LBBB	0.22 (0.20 – 0.24)
Lack of chest pain on examination	0.22 (0.21 – 0.24)
Age >75 years	0.40 (0.36 – 0.43)
Female sex	0.88 (0.83 – 0.92)

“late” reperfusion was nevertheless associated with a mortality benefit. Similar effects have been observed with tPA.¹⁵

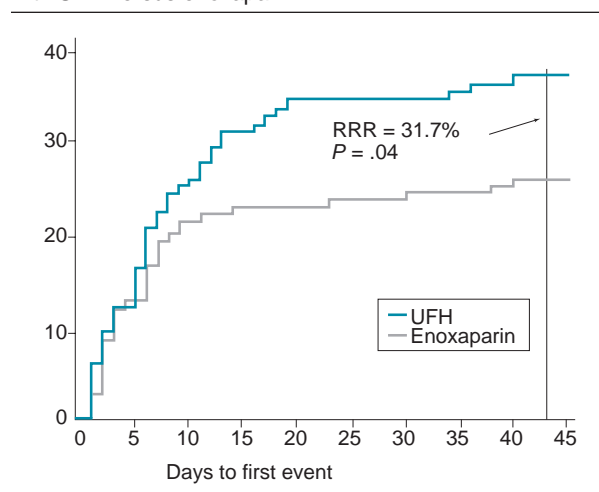
In one of the very few randomized trials using PCI in this population, Horie et al,¹⁶ randomized 44 patients with STEMI to reperfusion from 24 hours up to as long as 3 weeks after anterior wall Q wave MI, versus 39 non-PTCA controls. At 5-year follow-up, the PCI patients had significantly fewer cardiac events (4 vs 19, $p<0.0001$), and new CHF (1 vs 10, $p=0.002$). Pfisterer et al¹⁷ also found benefit from PTCA performed late after STEMI. Patients were randomized to early PCI performed up to 17 days post-MI (immediate group) or “delayed” PCI after 3 months of medical therapy. Significantly higher LVEFs and smaller LV end-systolic and diastolic volumes were seen in the immediate group compared to the delayed group. It appeared that PCI and reperfusion was preventing LV dilatation. The prospective, randomized Medicine versus Angiography in Thrombolytic Exclusion (MATE) Trial¹⁸ found that allocation to immediate angiography reduced the in-hospital ischemic event rate among patients ineligible for thrombolysis. However, there was no long-term reduction in rehospitalization rates, repeat angiography, late revascularization, recurrent MI, or death.

Post-hoc analyses: There is evidence that patients who spontaneously reperfuse retain better LV function than those whose infarct-related artery remains occluded, even though in such patients any intrinsic thrombolytic mechanisms normally take effect too late for substantial myocardial salvage.¹⁹⁻²¹ Late coronary reperfusion, when myocardial salvage is no longer likely, appears nevertheless to be associated with reduced LV dilatation, LV remodeling and aneurysm formation. Even if LV function is not grossly improved, mortality may be reduced.¹

In analyses of the Survival and Ventricular Enlargement (SAVE) trial,²² Lamas et al observed that in the 784 patients who had been revascularized by any means (thrombolysis, PTCA, CABG or CABG following unsuccessful PTCA), there was a lower mortality, 14% vs 24%, ($p<0.001$), compared to the 162 patients whose artery remained closed. Data from the German MITRA and MIR registries of 848 STEMI patients was suggestive of an in-hospital benefit when PTCA was performed after a pre-hospital delay of 12 to 24 hours. This difference did not remain significant in the multiple regression analysis.²³ This was similar to the experience of Elad et al.²⁴ Further evidence of the value of later reperfusion came when myocardial salvage was assessed in patients who had been stented and treated with abciximab as primary therapy for STEMI.²⁵ The proportion of perfusion defect that was salvaged in patients treated <12 hours after onset was very similar to that observed in patients treated after 12 hours.

In contrast, Brodie et al²⁶ observed that when PTCA was performed up to 2 hours following onset of pain, it was associated with lower 30-day and late cardiac mortal-

Figure 2: Kaplan-Meier curves for recurrent ischemic events occurring after admission with Q-wave MI treated with UFH versus enoxaparin²⁸



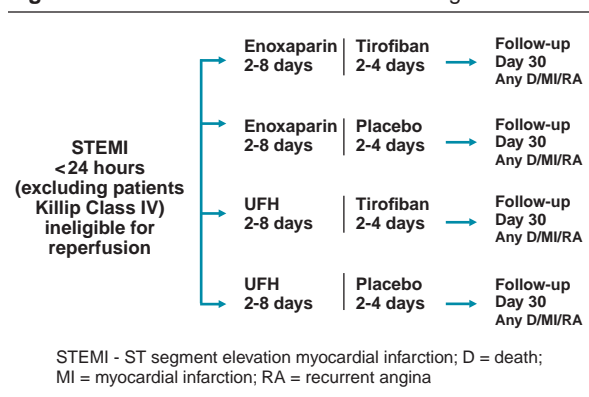
ity and better ventricular function than when performed 2-12 hours after onset. These findings are similar to those of Sheiban et al,²⁷ who found that preservation of LV function was strongly time-dependent, while prevention of LV remodeling was less so, among a cohort of PTCA patients (n=95) with a patent IRA at 6 months. PTCA salvaged myocardium only when performed < 4 hours after onset of pain. However, PTCA done > 6 hours after pain onset appeared to prevent LV remodeling and dilatation by preventing increases in end-diastolic volume index (EDVI) and end-systolic volume index (ESVI).

Non-lytic antithrombotic therapy in STEMI

The meta-analysis²⁸ of the ESSENCE and TIMI 11B trials established that the low molecular weight heparin (LMWH) enoxaparin is the preferred antithrombotic for acute treatment. Post-hoc analysis²⁹ of the 7,000 patients was performed on a subset of patients originally included in these trials who subsequently developed Q-wave myocardial infarction (QWMI) after enrollment and randomization. These patients initially had nondiagnostic ECGs and were therefore not candidates for reperfusion. Of these, 252 (3.6% of the total) were randomized to enoxaparin (n=137) or unfractionated heparin (UFH) (n=115). The substudy showed a consistent reduction in recurrent cardiac events with enoxaparin at all time points during QWMI (Figure 2). The day 43 composite triple endpoint was statistically lower in the enoxaparin group (RRR 31.7%, $P=0.04$). More recently, clinical trials with streptokinase,³⁰ alteplase,³¹ and tenecteplase,³² have all demonstrated the therapeutic value of enoxaparin as adjunctive therapy to thrombolysis in STEMI.

The Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) study,³³ evaluating the gly-

Figure 3: The TETAMI randomized trial design³⁵



coprotein (GP) IIb/IIIa blocker tirofiban in UA/NSTEMI, found that this antiplatelet drug increased the beneficial effect of heparin on ischemic events. Moreover, angiographic assessment of thrombus burden showed that the proportion of patients with medium/large/fresh occlusive thrombus was reduced from 24.1% among heparin-treated patients to 17.1% with the combination (overall odds ratio 0.77, $P=0.02$). Having been shown separately to reduce cardiac events when compared to UFH in UA/NSTEMI,^{28,33} two studies examined the proposition that the combination of tirofiban and enoxaparin offers further benefit.^{34,35} The larger study,³⁴ in which 525 UA/NSTEMI patients were randomized to tirofiban plus either aPTT-adjusted UFH (n=210) or enoxaparin (n=315), showed that TIMI bleeding and transfusion requirements were similar for the two regimens, but that total ischemic events were reduced in the enoxaparin group (11.4% vs 20.5%).

The next step

The ongoing TETAMI study³⁵ was conceived with a 2x2 factorial design to examine the effect of enoxaparin versus UFH, with and without tirofiban, in STEMI patients who were not eligible for reperfusion therapy. The primary endpoint is the composite of death/MI/recurrent angina; use of PCI is a secondary endpoint. Based on previous studies, 1200 patients were enrolled to enable an 80% power to detect a 30% relative reduction in the triple endpoint. Non-inferiority is being assessed if no superiority is detected. Once enrolled, patients receive enoxaparin or UFH for 2-8 days, and tirofiban or matching placebo (Figure 3). Patients ineligible for the study are included in a registry and their course followed to assess use of reperfusion. The most common reason for not using thrombolysis is late presentation (>12 hours), while in two-thirds of the cases where PCI is not performed, the main reason is lack of availability of suitable staff or a catheter laboratory (Figure 4).

Overall efficacy: Twenty per cent of TETAMI patients are treated or hospitalized within 12 hours of onset of

Figure 4a: Reasons for non-use of thrombolytics in the TETAMI study

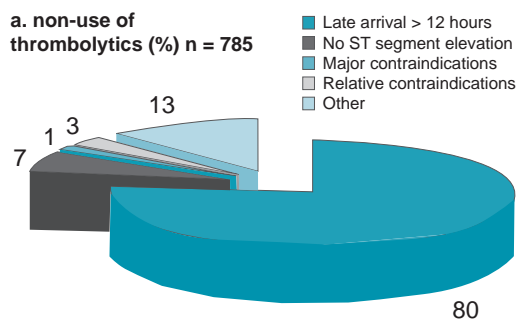
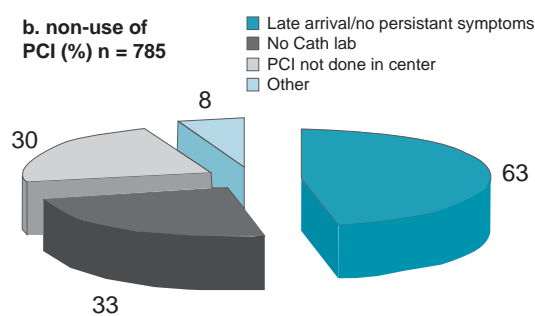


Figure 4b: Reasons for non-use of direct PCI in the TETAMI study



pain; 95% of the reperfused patients and 61% of those not reperfused present within 12 hours. Overall, the clinical event rate is highest in the registry of non-reperfused patients and lowest among the reperfused patients. There is a similar pattern for death, recurrent MI, and for the double endpoint, but CABG and PCI rates are highest among TETAMI patients (Figure 5).

Overall safety: Safety data appear to be comparable with those from GUSTO V,³⁶ in which all hemorrhage, major hemorrhage, and hemorrhagic stroke occurred in 25%, 4% and 1% of patients, respectively. Corresponding figures from TETAMI are 17%, 4%, and 0%, respectively. Thrombocytopenia has occurred in 1% of patients so far, the same proportion as in GUSTO V (Figure 6). Overall, the double endpoint has occurred in 66 (9%) of patients. Based on these overall aggregate data, one may conclude that the major reason for non-use of reperfusion is late presentation (>12 hours); Prospectively-enrolled TETAMI patients experience an event rate that is higher than reperfused patients, even when adjusting for Killip Class. Non-reperfused and nonenrolled patients have the worst prognosis. It is hoped that

data from the ongoing TETAMI study will help define optimal treatment patterns for patients unsuitable for reperfusion therapy.

Non-lytic non-antithrombotic therapy in STEMI: Cardioprotectants

The cardioprotective effects of AMP579, a mixed adenosine A1 and A2 agonist, were evaluated in the AMP579 Delivery for Myocardial Infarction REduction (ADMIRE) study.³⁷ Patients (n=321) with acute STE anterior or non anterior MI, presenting within 6 hours of onset of ischemia, were assigned to undergo PTCA. Whilst the drug did not appear to influence the outcome measures, patients receiving the higher doses of AMP579 (30 u/kg and 60 u/kg) displayed a trend towards smaller infarct size and greater myocardial salvage.

The transmembrane sodium/hydrogen ion exchanger (NHE) is responsible for the maintenance of myocardial pH during ischemia, although this process may paradoxically contribute to myocardial cell necrosis through promoting Ca⁺⁺/Na⁺ exchange. Cariporide was developed as a potent and specific inhibitor of the NHE.

Figure 5: Clinical events (efficacy) at 30 days in the TETAMI study

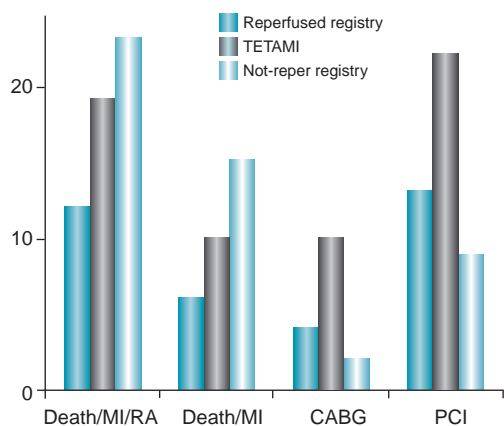
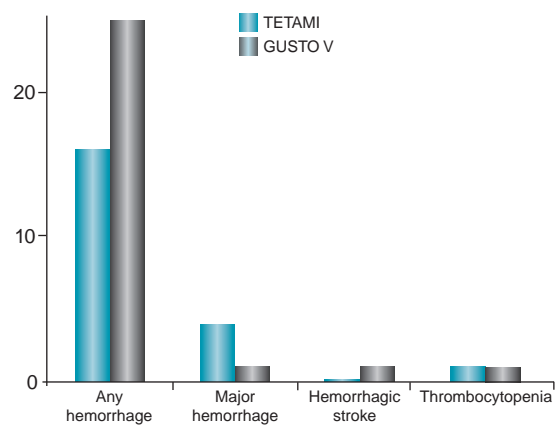


Figure 6: Safety events at 30 days; TETAMI compared to GUSTO V



The GUARD During Ischaemia Against Necrosis (GUARDIAN) trial was the first trial to assess the possible beneficial effects of inhibiting sodium-hydrogen exchange during myocardial ischemia.³⁸ 11,590 patients with UA/NSTEMI, or who were undergoing high-risk surgical revascularization procedures, were randomized to placebo or to 1 of 3 doses of cariporide for the period of risk. Primary endpoints were the composite of death/MI assessed at day 36. None of the trial doses had any effect on this endpoint. However, the highest dose of cariporide (120 mg) did appear to reduce risk – chiefly of nonfatal MI – among the cohort of CABG surgery patients. A similar lack of efficacy for another NHE inhibitor, eniporide, was demonstrated in the Evaluation of the Safety and Cardioprotective effects of eniporide in AMI (ESCAMI) trial.³⁹

Based on animal data showing the effects of anti-leukocyte antibodies on infarct size, the LIMIT-AMI trial⁴⁰ has evaluated the effects of the monoclonal antibody rhuMAb Cd18, directed against leukocyte adhesion. In addition to thrombolysis with tPA, 394 STEMI patients presenting within 12 hours of onset were randomized to receive the antibody or placebo. Unfortunately, the treatment had no effect on coronary blood flow, infarct size, or rate of ST segment resolution.

Summary and conclusions

Although the benefits of reperfusion are very time-sensitive, we must nevertheless be prepared to extend the period if benefits can be achieved. There no longer appears to be any reason not to attempt reperfusion up to 12 hours from the onset of symptoms. Beyond this window, PCI data suggest benefit, but not unequivocally. Once 12 hours have elapsed, aggressive antithrombotic therapies may represent the most promising avenue since, somewhat disappointingly, non-thrombosis-related “cardioprotectants” to-date appear to be almost uniformly ineffective. It therefore seems appropriate to re-examine the accepted time-window for later reperfusion. While it may not necessarily save myocardium, it may bring about other worthwhile benefits. This premise is the basis of the NIH-sponsored Open Artery Trial (OATS). Beyond myocardial salvage, a patent IRA and myocardial reperfusion seem to confer hemodynamic, LV remodeling, and other benefits. Since late presentation and non-STEMI constitute such a large proportion of AMIs, investigative approaches to improve management strategies of these non-lytic patients has become a prominent focus of AMI research.

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Dr. Cohen has authored or co-authored more than 200 articles, including 88 peer-reviewed papers and abstracts, as well as consulted on manuscripts for peer-reviewed journals, such as the *New England Journal of Medicine*, *Circulation*, *Journal of the American College of Cardiology* and others. He is a member of the editorial board of the *Journal of the American College of Cardiology*, the *American Journal of Cardiology*, and the *Journal of Thrombosis and Thrombolysis*. He also has contributed chapters on cardiology for several books including, "Unstable Angina: Antithrombotics and Thrombolytics" and "Prevention and Treatment of Unstable Angina."

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