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Scientific Update™

Treatment for ST-Elevation Myocardial Infarction An Update on Facilitated PCI trials and the Upcoming ACC/AHA STEMI Guidelines

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Over the last several years, significant advances have been made in mechanical and pharmacological reperfusion strategies for the treatment of ST-segment elevation myocardial infarction (STEMI). Based on these advances in the field, the American College of Cardiology (ACC) and the American Heart Association (AHA) have updated their 1999 Guidelines for Acute Myocardial Infarction[1] with newer recommendations focused specifically on STEMI. The updated guidelines are expected some time in 2004. At the recent ACC meeting in New Orleans, several members of the committee discussed some areas where the guidelines have been updated, outlined the issues that were considered, and presented the evidence that went into developing the new recommendations. This issue of *Cardiology Scientific Update* reviews some of the new information in the updated guidelines, including the use of guideline-recommended adjunctive antithrombotic therapy following thrombolysis, the benefits of primary angioplasty for STEMI, and evidence for angioplasty after thrombolysis. In STEMI, urgent delivery of reperfusion therapy (thrombolysis and/or angioplasty) is essential to restore anterograde flow in the infarct-related artery (IRA) and thereby limit infarct size and reduce subsequent morbidity and mortality. There has been considerable interest in combining thrombolysis and early angioplasty in a strategy termed facilitated percutaneous coronary intervention (PCI).[2] Two studies of facilitated PCI presented at the ACC meeting – the CAPITAL-AMI trial and the GRACIA-2 trial – will also be discussed in this issue.

Pharmacological reperfusion strategies

At the STEMI Guidelines symposium, the adjunctive use of antithrombotic therapy after thrombolysis was reviewed.[3] The 3 classes of antithrombotic therapy include fibrinolytic, antithrombin, and antiplatelet agents.

Lytics

Prompt administration of fibrinolytic agents remains the predominant reperfusion therapy for most hospitals since the majority of hospitals in Canada and North America do not have on-site cardiac catheterization facilities. A meta-analysis of 9 trials involving 58,600 patients demonstrated that thrombolytic therapy results in a 3% absolute reduction in 30-day mortality when administered within 6 hours of symptom onset.[4] However, for each hour of delay in treatment, the mortality benefit was reduced by 1 life per 1000 patients treated.[4] The new guidelines emphasize the importance of rapid treatment, and review the evidence for pre-hospital diagnosis and thrombolysis.[5,6] The new ACC/AHA recommendations will likely be similar to the recently published European guidelines, which recommend that

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thrombolysis be initiated within 30 minutes of hospital arrival or within 90 minutes of the patient calling for medical treatment.[7]

Aspirin

Aspirin has been clearly shown to improve outcomes after thrombolysis and, when added to streptokinase, was associated with a 42% reduction in mortality in the ISIS-2 trial.[8] Angiographic trials have demonstrated that aspirin reduces the reocclusion rate after myocardial infarction (MI). On the basis of these and other observations, the use of aspirin for STEMI will receive a Class 1 recommendation in the new guidelines. Recent studies, including a subgroup analysis from the CURE trial, have suggested that lower doses of aspirin have similar efficacy and a more favourable safety profile than higher doses.[9,10] The new guidelines therefore will likely recommend lower long-term maintenance doses of aspirin (75-162 mg per day).

Clopidogrel

For patients who have true contraindications to aspirin, clopidogrel has been shown to be an effective alternative antiplatelet agent. Although there is clinical trial evidence for the benefit of clopidogrel combined with aspirin in non-ST elevation myocardial infarction (NSTEMI),[11] there are presently no data on the safety and efficacy of this combination for STEMI, particularly if a fibrinolytic agent is used. Ongoing trials such as the CLARITY-TIMI-28 trial should provide definitive data on the role of dual antiplatelet therapy in this setting.

GP IIb/IIIa agents plus fibrinolysis

Since the earlier guidelines were published, there have been a number of studies that have evaluated the combination of half-dose fibrinolytic agents and glycoprotein (GP) IIb/IIIa inhibitors.[12] Although initial studies suggested that this combination resulted in higher rates of patency and TIMI-3 flow in the IRA compared with full-dose fibrinolysis alone,[13,14] subsequent studies have shown no difference in TIMI-3 flow rate.[15] This may explain why no difference in mortality was observed in larger trials such as GUSTO-5 and ASSENT-3.[16,17] Combination therapy also resulted in higher rates of major bleeding and a disturbing trend toward increased intracranial hemorrhage in elderly patients. As a result of these disappointing findings, combination therapy with half-dose fibrinolytics and GP IIb/IIIa inhibitors will likely not receive a very high recommendation in the new guidelines.

A recent study by Dr. Giugliano evaluated outcomes when GP IIb/IIIa inhibitors are used during PCI soon after full-dose fibrinolysis. As seen in previous studies,[18] the use of GP IIb/IIIa inhibitors in this setting is associated with a significant increase in major bleeding, particularly if they are started within 3-6 hours after fibrinolysis.

Unfractionated heparin

Although unfractionated heparin (UFH) has been the standard antithrombin therapy for STEMI, there is still uncertainty about the optimal use of UFH as an adjunct to thrombolytic therapy. UFH has clearly been shown to improve the patency rates of the IRA when combined with tissue plasminogen activator (tPA); however, there has been controversy on its role when streptokinase is used. Although it is not possible to answer this question definitively, the guideline committee noted that in a recent meta-analysis, UFH was associated with a significantly lower rate of death and reinfarction.[19] Although the benefit was greatest in older trials that did not routinely use aspirin, the benefit remained significant even when aspirin was used. Accordingly, the use of UFH as an adjunct to streptokinase will likely be upgraded from a Class III recommendation in the older guidelines to a Class II recommendation in the newer guidelines. There have been changes in the dosing of UFH combined with fibrin-specific fibrinolytic agents. In the GUSTO-1 trial, bleeding and mortality were increased with higher partial thromboplastin time (PTT) values.[20] The use of a weight-adjusted bolus and infusion of UFH with fully weight-adjusted tenecteplase (TNK) has been shown to have a more favourable safety profile in the ASSENT-3 trial.[17] As a result, the new guidelines will recommend that UFH be administered as a weight-adjusted bolus of 60 U/kg (maximum 4000 U), followed by an infusion of 12 U/kg (maximum 1000 U/hour) for 48 hours after thrombolysis, with a target PTT of 50-70 seconds.

Alternative agents

There is growing interest in alternative antithrombin agents, including direct antithrombins, low molecular weight heparin (LMWH), and pentasaccharides. All of these agents have pharmacological properties that lead to more potent and predictable inhibition of thrombin formation and thrombin activity. A meta-analysis of the 11 direct thrombin inhibitor trials was recently performed in >35,000 patients.[22] This included 5 trials (approximately 10,000 patients) of STEMI. The 3 direct thrombin inhibitors evaluated were argatroban, hirudin, and bivalirudin. By the end of the study-drug treatment (approximately 3 days), there was a trend toward reduced death and reinfarction that was not statistically significant and was driven mainly by a reduction in reinfarction. By 30 days, this benefit had diminished, suggesting a possible rebound effect after these agents were discontinued. The HERO-2 trial directly compared UFH with bivalirudin in patients with STEMI treated with streptokinase.[23] Bivalirudin was associated with a significant reduction in reinfarction, significantly higher rates of bleeding, and no difference in mortality. Enoxaparin is being compared with UFH in the ongoing EXTRACT-TIMI-25 trial, the first trial to evaluate an adjusted dosing regimen in patients >75 years who will receive 75% of the usual maintenance subcutaneous enoxaparin dose and no initial intravenous bolus. In the OASIS-6 trial, fondaparinox, a pentasaccharide agent, will be compared to UFH or placebo in patients receiving thrombolysis. At present, no firm recommendations can be made on the use of these alternative antithrombin agents as adjuncts to thrombolysis.

Mechanical reperfusion strategies

The new guidelines will also provide an update on mechanical reperfusion strategies. In the 1999 guidelines, primary PCI was recommended as a suitable alternative to thrombolysis, but limited data were available at that time. Adjunct PCI after thrombolysis was not recommended and rescue PCI for failed thrombolysis received modest support. Routine elective PCI after successful thrombolysis and prior to hospital discharge was not recommended, based on negative findings in older trials. The new guidelines will include updated sections and recommendations on the use of primary PCI in cardiogenic shock, the strategy of transferring patients for primary PCI, and facilitated PCI.

Primary PCI in cardiogenic shock

The SHOCK trial randomized patients with MI complicated by cardiogenic shock to emergent revascularization or initial medical stabilization. Emergent revascularization was associated with a trend toward lower mortality at 30 days and a significantly lower mortality at 6 months and at one year.[24,25] The benefit of early revascularization –13 lives saved per 100 patients treated – represents the largest mortality reduction in STEMI since defibrillators were released in the 1960s and is similar to the benefit for bypass surgery in patients with left main coronary artery disease. Despite these findings and a Class I recommendation in the earlier guidelines, there has been no obvious increase in the use of PCI for patients in cardiogenic shock. The new guidelines will reinforce the importance of performing early revascularization in patients within 12 hours of onset of cardiogenic shock.

Primary PCI

A recent meta-analysis comparing primary PCI with thrombolysis included 23 trials and >7,700 patients.[26] In this meta-analysis, primary PCI was associated with a significantly lower rate of death (5% vs. 7%; p=0.0003), reinfarction (3% vs. 7%; p<0.0001), and stroke (1% vs. 2%; p=0.0004) as compared to thrombolysis. When the mortality analysis was limited to trials of fibrin-specific lytics, the relative and absolute differences in mortality were lower in magnitude. Furthermore, the heparin doses used for thrombolysis were excessive when compared with contemporary guidelines and this may have contributed to the higher stroke rates. Furthermore, the high rates of reinfarction after thrombolysis may have been prevented with more potent antithrombotic therapy (eg, LMWH) or more liberal use of rescue PCI for recurrent ischemia.

Five of the trials (including the DANAMI-2 trial[27]) included patients who required transfer for primary PCI. The outcomes with primary PCI vs. thrombolysis in patients who required transfer were similar to that seen in the overall meta-analysis. The largest differences in mortality were seen in the older trials that used streptokinase. The mortality rates seen after thrombolysis were higher than those seen in many other trials and registries of STEMI and may be potentially related to selection bias. These and other factors may have led to an overestimation of the difference in outcomes between the 2 strategies.

Several studies have revealed that outcomes after PCI are related to operator and institutional case volumes.[28] This will be reflected in the updated guidelines, which will recommend a minimum institutional volume of 36 primary PCI angioplasties per year and a minimum operator total volume of 75 angioplasties per year.[29]

The most contentious issue for the guideline committee is the optimal "door-to-balloon time." Most studies have indicated that the higher mortality observed after primary PCI is associated with significant delays between symptom onset or hospital presentation and the first balloon inflation.[30-33] The previous guidelines suggested that a door-to-balloon time of up to 120 minutes would be reasonable. However, the best outcomes are achieved when the first balloon inflation occurs within 90 minutes of the first medical contact. The committee recognizes that a recommendation of ≤90 minutes between the first medical contact and balloon time may be problematic for many hospitals since registries have shown that this high standard is achieved only in a minority of cases.[30] However, Dr. Bates stressed that the guideline recommendations are not meant to be used as legal or regulatory standards.

Time delays for primary PCI appear to be most detrimental in the highest risk patients.[34,35] One study demonstrated that outcomes after primary PCI performed overnight are worse than when performed during daytime hours.[36] It is unclear whether this is related to biological diurnal variation, treatment delays, or sleep deprivation. The new guidelines will recommend that institutional and regional reperfusion strategies be developed that take into account the time from symptom onset to presentation, the time required to transfer the patient for primary PCI, and the risk profile of the patient.

Therefore, the benefits of primary PCI may not be achieved with low-volume operators or hospitals, off-hour procedures, delayed door-to-balloon times, or in patients with symptom onset <3 hours.[37,38] Some studies have also shown less benefit in younger patients and patients with inferior STEMI.

Facilitated PCI

Facilitated PCI involves treating STEMI patients with pharmacological reperfusion followed by immediate angioplasty of the IRA. Intuitively, this would seem to be the best reperfusion strategy as it would achieve the same high rates of TIMI-3 flow and low rates of reocclusion and recurrent ischemia as primary PCI, without the treatment delay. Observational studies have shown that patients undergoing primary PCI who are found to have a patent IRA prior to balloon inflation have better left ventricular wall motion and ejection fraction, higher rates of PCI success, less heart failure, and lower mortality.[39,40] Several small trials have been presented,[41] including the CAPITAL-AMI and GRACIA-2 trials (discussed below). So far, none of these trials have demonstrated any improvement in ejection fraction, infarct

size, or mortality. However, their sample sizes were very small and, therefore, definitive recommendations on facilitated PCI cannot be made at this time. Several large trials are underway, including FINESSE, ASSENT-4 PCI, WEST, and TRANSFER-AMI, that should help clarify the recommendations.

The CAPITAL-AMI trial

The preliminary results of the Combined Angioplasty and Pharmaceutical Intervention versus Thrombolysis Alone in Acute Myocardial Infarction (CAPITAL-AMI) study were recently presented at the ACC meeting. The study enrolled 170 patients with STEMI within 6 hours of symptom onset, with at least 1 of the following high-risk characteristics: ≥2 mm ST-elevation in the anterior leads, non-anterior STEMI with extensive ST-elevation/depression, Killip class 3, or hypotension. Patients with cardiogenic shock, previous bypass surgery, or PCI within 6 months were excluded. The primary endpoint was the composite of death, reinfarction, recurrent unstable ischemia, and stroke at 30 days. Patients were randomized to receive either thrombolysis alone (full-dose tenecteplase with weight-adjusted UFH) or thrombolysis followed by immediate transfer for coronary angiography and possible revascularization.

Among the 86 patients randomized to facilitated PCI, 85 underwent early angiography and 79 underwent PCI (stenting in all but 2). The IRA was persistently occluded in 15% of cases. The average time between tenecteplase administration and the first balloon inflation was 90 minutes. TIMI grade 3 flow was achieved in 89% of cases. Non-protocol angiography was performed in 67% of patients in the thrombolysis alone group during the initial hospitalization, with revascularization in 48%. Results of selected endpoints are shown in Figure 1. During the initial hospitalization, there were no significant differences in the death or stroke rates, but facilitated PCI was associated with significantly lower rates of reinfarction (3.5% vs. 11.9%; p=0.046) and recurrent unstable ischemia (5.8% vs. 17.9%; p=0.02). At 30 days, the incidence of recurrent ischemia remained significantly lower with facilitated PCI, but the difference in reinfarction was no longer statistically significant. The composite primary endpoint was significantly lower with facilitated PCI (9.3% vs. 21.4%; p=0.03). There were no significant differences in major bleeding (8.3% with TNK alone, 9.3% with facilitated PCI) or transfusions (2% vs. 6%). There were no significant differences in the ejection fractions (by radionuclide angiography) at 1 week or at 30 days. The hospital length of stay was on average 1 day shorter with facilitated PCI (5 vs. 6 days, p=0.009).

In summary, the CAPITAL-AMI trial demonstrated that facilitated PCI after full-dose tenecteplase is safe, feasible, and associated with lower rates of reinfarction and recurrent ischemia compared with thrombolysis alone.

The GRACIA-2 trial

The GRupo de Análisis de la Cardiopatia Isquémica Aguda (GRACIA-2) trial compared facilitated PCI with primary PCI. The study was carried out at 15 centres in Spain and Portugal and enrolled 212 patients with STEMI within 12 hours of symptom onset. Patients were randomized to undergo either primary PCI within 180 minutes or facilitated PCI within 12 hours of treatment with tenecteplase and enoxaparin. The 3 primary endpoints were the infarct size (estimated by CK-MB and troponin release), ST-segment resolution, and left ventricular size and function at 6 weeks. Abciximab was used in 87% of patients in the primary PCI group and 23% of patients in the facilitated PCI group (p=0.001). The average times from randomization to catheterization were 1.1 hours for primary PCI and 5.9 hours for facilitated PCI (p=0.001).

Results of selected endpoints are shown in Figure 2. As expected, the incidence of initial infarct artery occlusion at the time of angiography was significantly higher in the

Figure 1: The CAPITAL-AMI Study

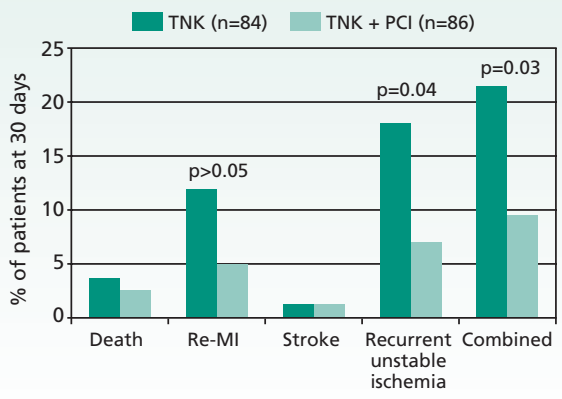

Figure 2: GRACIA-2 Study

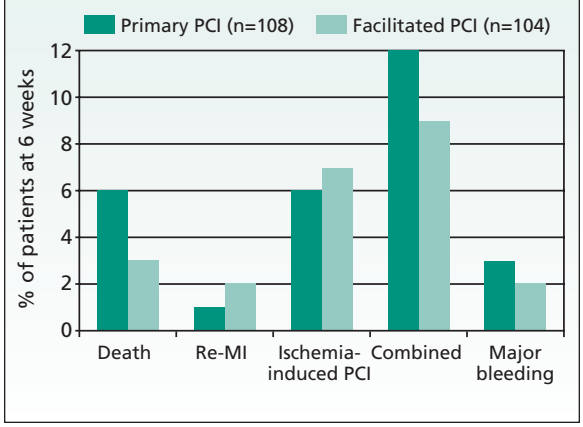

Figure 3: Reperfusion options for STEMI

Fibrinolysis generally preferred

Primary PCI not an option
- Cath lab occupied / not available
- Vascular access difficulties
- No access to skilled PCI centre

Delay to Primary PCI
- Prolonged transport
- Door to Balloon >90 min
- >1 hr vs. lysis now

Very early presentation
- <1-2 hrs from symptoms

Primary PCI generally preferred

Skilled centre available / short delay
- Operator experience ≥75 cases/yr
- Team experience ≥36 1° PCIs/yr
- Door to Balloon <90 min

High risk from MI
- Cardiogenic shock (age <75 yrs)
- Killip class ≥2

Increased bleeding risk
- Especially ICH

Late presentation
- >2-3 hrs from symptoms

Diagnosis in doubt

Adapted from Armstrong, et al[42]

primary PCI group (73% vs. 8%; p=0.008). The proportions of patients with complete ST-segment recovery were similar at 1 hour and 3 hours, but at 6 hours, complete ST-segment resolution occurred more often with facilitated PCI (61% vs. 43%; p=0.03). There were no significant differences in CK-MB or troponin release, left ventricular function, or left ventricular dimensions at 6 weeks. The incidence of death, reinfarction, urgent surgery, repeat PCI for ischemia, and the composite were very similar between the 2 groups. There were no significant differences in the rates of major bleeding (3% for primary PCI vs. 2% for facilitated PCI). Angiography was repeated at 6 weeks, and there were no significant differences in IRA patency, flow, or myocardial perfusion. Compared with primary PCI, facilitated PCI resulted in similar clinical and angiographic outcomes with no increase in bleeding complications and more complete ST-segment resolution at 6 hours. The investigators recommend that facilitated PCI be considered in STEMI when primary PCI cannot be performed within 120 minutes of first medical contact.

Conclusion

The management of STEMI continues to evolve. Although the role of primary PCI has expanded to include patients requiring transfer, the optimal reperfusion strategy for individual patients will depend on clinical characteristics (duration of symptoms, infarct location, hemodynamic status, risk of severe bleeding), institutional and regional factors (estimated medical contact to balloon time, physician and hospital PCI volumes), and possibly, time of day (Figure 3). Facilitated PCI appears to be a promising reperfusion strategy and may achieve the benefits of primary PCI without delaying treatment. Although several small trials have shown favourable outcomes compared with primary PCI and with thrombolysis alone, larger studies are needed to determine the safety, efficacy, and cost-effectiveness of this approach before it can be incorporated into routine clinical practice. Regardless of the reperfusion strategy used, clinical outcomes are improved with the optimal use of weight-adjusted adjunct pharmacotherapy, long-term secondary prevention with aspirin, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, statins, and risk factor modification.

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