Primary coronary intervention in acute myocardial infarction

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Percutaneous coronary intervention (PCI) with stent implantation has become the standard of care for acute myocardial infarction < 12 hours from symptom onset. This has led to decreased morbidity and mortality both short and long term compared to thrombolytic therapy. Stent implantation has been demonstrated to be superior to balloon PCI for mechanical reperfusion of acute myocardial infarction. Intravenous antiplatelet glycoprotein IIb/IIIa inhibitors may have a role in improving TIMI flow prior to PCI and decreasing morbidity and mortality. The role of thrombolytics vs IIb/IIIa inhibitors in "facilitated reperfusion" is unclear at this time and further research is needed to define the indication of adjunctive pharmacology.

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While the rate of mortality has decreased in the last two decades, cardiovascular disease still causes over 17 million deaths worldwide. This review focuses on the acute management of ST-elevation myocardial infarction (STEMI), highlighting key research that has shaped the evolving science of catheter-based reperfusion therapy.

Percutaneous coronary intervention versus thrombolytics

The current standard of care for STEMI is directed at reperfusing the infarcted or ischemic myocardial tissue by pharmacologic or mechanical techniques. The two main modalities of reperfusion therapy are percutaneous coronary intervention (PCI) and pharmacologic thrombolysis. Both resolutions of the obstructing lesion and restoration of TIMI flow 3 are optimal goals.

A recent meta-analysis showed that the combined endpoints of death and reinfarction were reduced from 16 to 11% at 6 months in the PCI group compared with thrombolysis[1]. At 30 days and 6 months, PCI was associated with lower mortality, reinfarction, and stroke than thrombolytic therapy (Fig. 1).

Long-term data also suggest that the mortality benefit is sustained through 5 years, with 13% all-cause mortality in the PCI group compared to 25% with thrombolytic therapy alone (Fig. 2)[2].

The data indicate the superiority of PCI over lytic therapy in trials with prespecified inclusion criteria to reduce mortality and morbidity from acute myocardial infarction. However, it is important to define the practical application of these data to global medical practice. The superior results depend on experienced operators performing a large volume of procedures[3]. This practice may not be feasible or possible in all hospitals, particularly in sparsely populated regions.

Time-to-treatment

In order to better understand the role of reperfusion, the relationship between time-to-treatment and outcome was assessed. In a meta-analysis of 22 randomized trials including 50 246 patients, pharmacologic thrombolysis < 2 hours from symptom onset had a significant mortality reduction compared to later treatment[4]. However, delays > 6 hours from symptom onset rendered the thrombolytic therapy ineffective. Clearly, the efficacy of reperfusion depends on this early treatment.

The correlation between mortality as a function of time from symptom onset to PCI is not as well correlated as thrombolytics. Using over 27 000 patients in the Second National Registry of Myocardial Infarction, Cannon et al.[5] found no relationship between mortality and symptom-onset-to-balloon time up to 12 hours. They

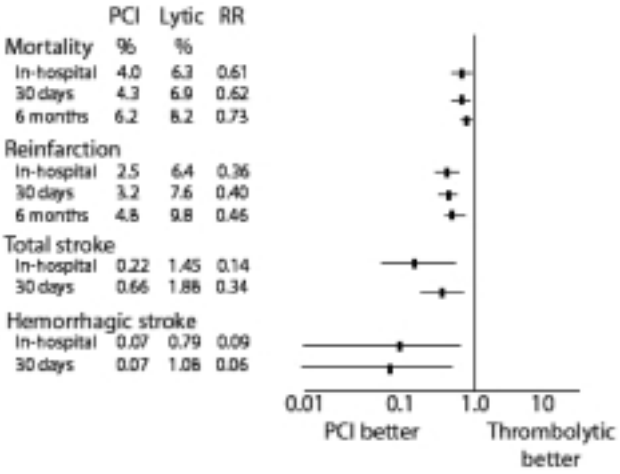

Figure 1. *Outcome comparisons at various time points. Lytic = thrombolytic; PCI = percutaneous coronary intervention; RR = relative risk. Adapted from Grines et al.[1].*

did find an increased risk of mortality if > 2 hours elapsed from emergency room presentation to PCI. Whether this represents more severely ill patients requiring stabilization prior to transfer for catheterization or a correlation between delay and worse outcome is unknown. However, these data suggest that PCI may be effective up to 12 hours after the onset of symptoms. This represents a significant extension from the narrow therapeutic window offered by thrombolytic therapy.

In the Stent-PAMI trial there was a 12% improvement in ejection fraction at 6 months for patients reperfused within 2 hours compared to 4% in those reperfused > 2 hours after symptom onset[6]. There was also an increased rate of reinfarction if > 4 hours elapsed between symptom onset to balloon inflation. However, there was no difference in mortality or target vessel revascularization at both 1 and 6 months.

More support for the lengthened therapeutic window of PCI emerged from a study performed at Northwestern University. The mortality and morbidity of patients presenting to the emergency department with STEMI during daytime hours was compared to "after-hours" – defined as weekends and after 7 p.m. weekdays. Despite an increase from symptom-onset-to-balloon time of 3.2 to 4.5 hours, there was no significant increase in mortality and morbidity at 3 years. This demonstrated that mechanical revascularization is similarly effective in the setting of "on-call" cardiac catheterization[7].

From these studies, PCI and thrombolytic therapy are most effective within 2 hours of symptom onset and less effective at > 4.5 hours. PCI improves short- and long-term survival over thrombolysis when time-to-treatment is equivalent. PCI retains efficacy up to 12 hours after symptoms, while thrombolysis does not.

More recently, the DANAMI-2 investigators randomly assigned 1572 patients with acute myocardial infarction to treatment with PCI or accelerated treatment with intravenous alteplase; 1129 patients were enrolled at 24 referral hospitals and 443 patients at 5 invasive-treatment centers. Patients presenting to referral hospitals were randomized to either initial stabilization and transfer to invasive-treatment centers for PCI or to accelerated intravenous alteplase. Patients randomized to PCI had a reduced incidence of death, reinfarction, or disabling stroke at 30 days (8.5 vs 14.2%, p = 0.002). The improved outcome was mainly due to reduced reinfarction rate (1.6 vs 6.3%, p < 0.001)[8]. It is important to note that transfers to invasive-treatment centers were to be completed within 2 hours of presentation with an available cardiac catheterization laboratory. The median time to thrombolysis was 2.8 and 2.7 hours for referral and invasive centers, respectively, and the time to PCI was 3.7 and 3.1 hours, respectively. The findings of DANAMI-2 illustrate that transfer of patients to referral centers for PCI is superior to thrombolysis if transfer can be accomplished in an expedited fashion.

Zahn et al.[9] set out to answer the question, "how late is too late for PCI?" They studied patients with symptoms between 12 and 24 hour duration. Since the

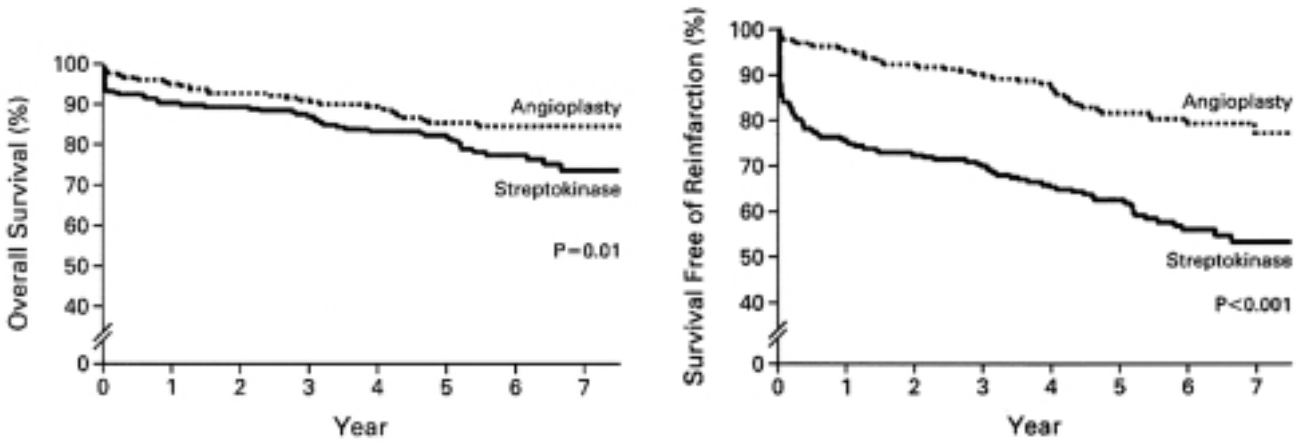

Figure 2. *Time-to-event analysis with percutaneous coronary intervention (PCI) vs thrombolysis. Adapted from Zijlstra et al.[2].*

study was not randomized, patients receiving PCI were significantly different from the conservatively treated patients. Mortality was 8.5% in the PCI group compared to 17% in those conservatively managed. This difference was not statistically significant after multiple logistic regression accounted for population differences.

Stent versus balloon percutaneous coronary intervention

Stent implantation has been shown to be superior to balloon for treatment of acute STEMI. Numerous small studies have shown superiority of stents to balloon angioplasty. In 1998, Suryapranata et al.[10] randomized 227 patients to stent compared to balloon PCI and found a significant decrease in recurrent myocardial infarction, target vessel revascularization, and the frequency of any cardiac event in the stent group. Antoniucci et al.[11] randomized 150 patients with angioplasty to stent vs no stent in the FRESCO trial. At 1 and 6 months, there were significantly less combined events in the stented group: death, reinfarction, or repeat target vessel revascularization. The reduction was attributed mainly to decreased recurrent ischemia (28 to 9%) in patients randomized to stent. Angiography supported these findings; restenosis and reocclusion were significantly lower in the stent group at 30 days and 6 months. In analyzing the non-stent patients with early reocclusion, it was observed that early recurrent ischemia was highly associated with occlusive or subocclusive coronary artery dissection. The authors postulated that stents stabilize arterial dissection and thereby lead to less early reocclusion.

In the PASTA trial, Saito et al.[12] randomized 69 patients to balloon PCI and 67 patients with primary stent implantation. All patients had acute myocardial infarction and were intervened within 12 hours of symptom onset. Major cardiac events (death, myocardial infarction, target vessel revascularization) were lower in the stent group at 6 months (6 vs 19%) and at 12 months (21 vs 46%). Angiographic restenosis rates at 6 months were also lowered from 37.5 to 17% in the stent group.

These findings were supported by Stent-PAMI. This larger trial enrolled 900 patients having STEMI with symptoms < 12 hours. Patients were randomized to balloon PCI with or without heparin-coated stent. At 1 and 6 months, there were significantly less patients needing target vessel revascularization for ischemia in the stent arm. Angiographically, there was less dissection immediately post-procedure with stents (11.9 vs 30.8%). At 1 and 6 months, stents decreased residual stenosis and resulted in larger minimal luminal diameter with decreased rates of late restenosis and reocclusion[13].

The FRESCO and PASTA trials were done without glycoprotein IIb/IIIa inhibitors, while Stent-PAMI had approximately 5% of patients on this adjunctive pharmacotherapy. The CADILLAC trial randomized 2082 patients in 2 × 2 factorial design to balloon PCI, PCI with abciximab, stent alone, or stent with abciximab. This large, multicenter study established PCI with stent as the standard of care. Patients had less need for ischemia-guided revascularization with stents over PCI alone at 1 (3.2 vs 5.6%, p = 0.004) and 6 months (8 vs 16%, p < 0.001) (Fig. 3)[14]. Stents were also associated with improved long-term angiographic results: patients with stent had increased mean luminal diameter and decreased residual stenosis than the non-stent controls. The overall rate of restenosis was 22.2% after stent compared to 40.8% after balloon PCI (p < 0.001), reocclusion of the infarct-related artery was cut from 11.3 to 5.7% (p = 0.01), and both rates were independent of

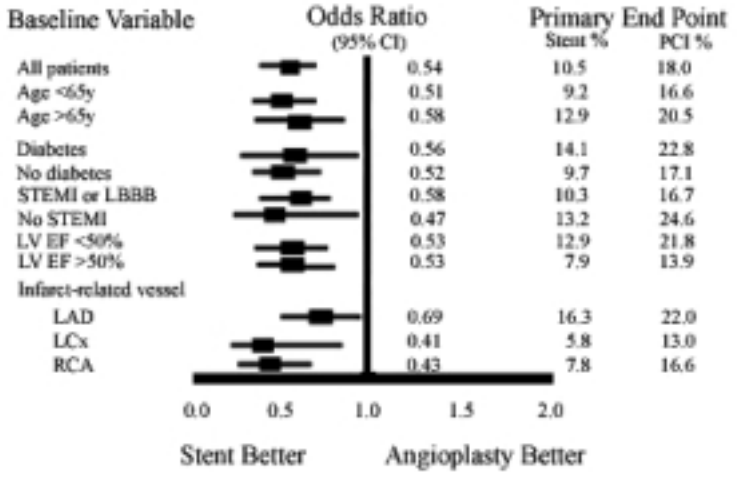

Figure 3. *Odds ratio of the primary composite endpoint of death, reinfarction, target vessel revascularization, and disabling stroke at 6 months. CI = confidence interval; LAD = left anterior descending coronary artery; LBBB = left bundle branch block; LCx = left circumflex coronary artery; LV EF = left ventricular ejection fraction; PCI = percutaneous coronary intervention; RCA = right coronary artery; STEMI = ST-elevation myocardial infarction. Adapted from Stone et al.[14].*

abciximab administration. In this study, the overall event rate was low and no additional benefit was obtained in patients who received abciximab if a stent was used.

To address whether decreased restenosis in CADILLAC was due to superior initial angiographic result or property of the metallic stent, a subgroup analysis evaluated "stent-like" or "optimal" balloon PCI vs stent. The authors concluded that even when angiographically similar at initial intervention, stenting reduced rates of ischemic target vessel revascularization at 1 year from 19 to 9% ($p < 0.001$)[15].

While CADILLAC patients were highly selected and complex lesions excluded, Antoniucci et al.[16] studied 201 consecutive patients with acute myocardial infarction and found similar results. With stents, angiographic restenosis decreased from 43 to 22% at 6 months and combined death, reinfarction, and ischemia-driven revascularization was 15% in a population that included age > 75 and cardiogenic shock.

A recently published subgroup analysis of CADILLAC suggests that stents have added utility and efficacy in failed balloon PCI. Of the 1044 patients randomized to balloon PCI, 168 had unsuccessful dilation and were crossed over to "bail-out" stents. Event-free survival was similar between bail-out and routine stent implantation and greater than after successful balloon angioplasty, indicating that bail-out stent is preferable to successful PCI without stent[17].

Drug-eluting stents

While only small studies are available comparing new drug-eluting stents to conventional metallic stents in acute myocardial infarction[18], evidence from SIRIUS suggests that sirolimus-eluting stents may further decrease angiographic stenosis and the need for target vessel revascularization[19]. Current research will soon clarify the role of drug-eluting stents in reducing the morbidity of acute myocardial infarction.

Role of glycoprotein IIb/IIIa inhibitors

Recent studies of glycoprotein IIb/IIIa inhibitors have helped clarify their role in PCI for acute myocardial infarction. In 2001, the ADMIRAL trial randomized 300 patients with STEMI to pre-PCI abciximab vs placebo. All patients received stents, but patients randomized to abciximab plus stent had > 50% lower composite endpoint (death, reinfarction, urgent target vessel revascularization) at 1 and 6 months ($p = 0.01$ and $p = 0.02$, respectively)[20]. Patients who received abciximab were > 3 times more likely to have TIMI 3 flow at the time of angiography ($p = 0.01$) and have higher left ventricular ejection fraction at 24 hours and 6 months after revascularization ($p \leq 0.05$). A secondary analysis of patients receiving abciximab in CADILLAC demonstrated a decrease in ischemic target vessel revascularization (relative risk 0.57, $p = 0.02$) and subacute thrombosis (relative risk 0.26, $p = 0.01$) at 30 days, but not at 1 year[21].

A cumulative meta-analysis of the 20 186 patients in ADMIRAL, CADILLAC, and 10 other studies concluded that in addition to less recurrent myocardial infarction and target vessel revascularization, there was a significant 30-day mortality reduction with IIb/IIIa inhibitors (odds ratio 0.73, 95% confidence interval 0.55-0.96, $p = 0.024$) (Figs. 4 and 5)[22]. While the magnitude of mortality reduction was similar at 30 days and 6 months (number needed to treat 357 vs 313), decreased power at 6 months resulted in loss of statistical significance. Larger trials may improve the power to detect differences at 6 months.

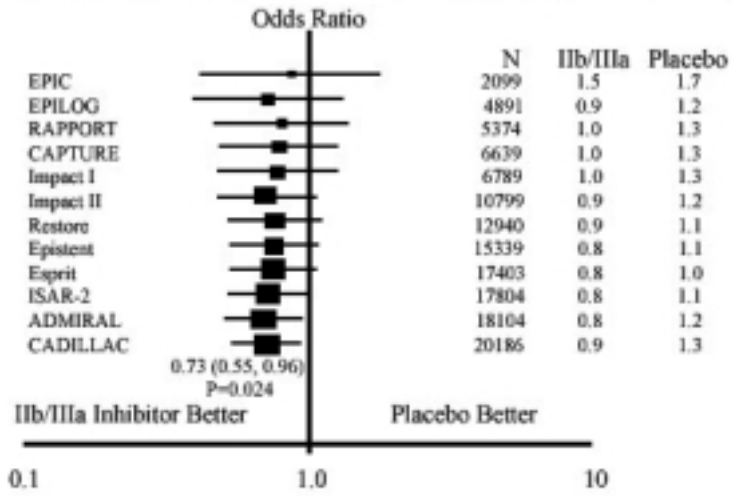

Figure 4. *Risk of death at 30 days after randomization to a glycoprotein IIb/IIIa inhibitor vs placebo in a cumulative meta-analysis. Cumulative event rates are listed for IIb/IIIa and placebo arms. Adapted from Kong et al.[22].*

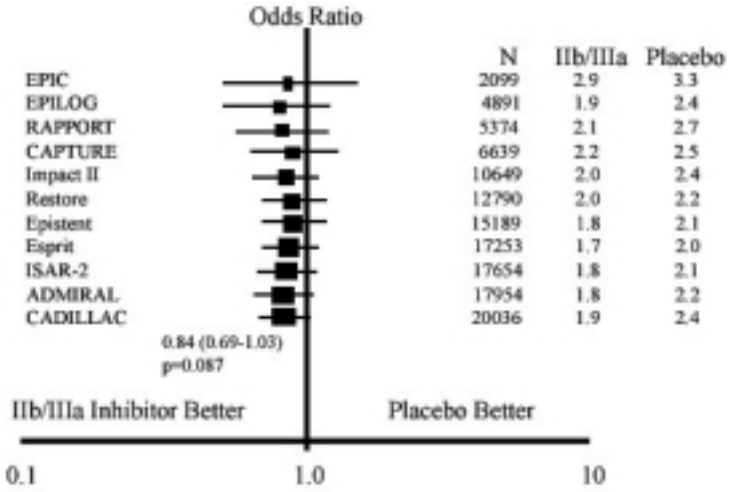

Figure 5. *Risk of death at 6 months after randomization to a glycoprotein IIb/IIIa inhibitor vs placebo in a cumulative meta-analysis. Cumulative event rates are listed for IIb/IIIa and placebo arms. Adapted from Kong et al.[22].*

Facilitated reperfusion

Adjunctive pharmacology is currently evolving into a facilitated reperfusion strategy. PCI with stents decrease mortality, reinfarction, and target vessel ischemia over traditional thrombolysis alone. Pooled data from the PAMI trials found that TIMI 3 flow *prior* to PCI was an independent determinant of survival (odds ratio 2.1, p = 0.04)[23]. However, the minority of hospitals worldwide have 24-hour catheterization laboratories available for immediate PCI. There may be an important role for pre-hospital or referral hospital administration of pharmacologic agents to maintain/restore TIMI 3 flow prior to PCI. In ADMIRAL, the patients receiving early abciximab had 16.8% TIMI 3 flow compared with 5.4% in the placebo group (p = 0.01)[20]. The SPEED trial employed early PCI preceded by abciximab, reteplase, or abciximab plus half-dose reteplase. PCI was performed within 90 min after administration, and patients with combination therapy (abciximab plus half-dose reteplase) had 47% pre-PCI TIMI flow 3 (abciximab alone was 24%, p = 0.05)[24]. It is unclear whether IIb/IIIa inhibitors, thrombolytics, or both will become a routine adjunct to mechanical intervention in the future.

Cost analysis

Studies have shown that PCI improves morbidity and mortality in STEMI over pharmacologic therapy alone. In addition, PCI allows better risk stratification, early discharge strategies after acute myocardial infarction, decreased in-hospital complications, and decreased rates of rehospitalization that help offset the initial operator costs[25]. When corrected for 2000-2001 pricing, Cohen et al.[26] estimate the 1 year difference in cost of PCI with stenting to be < $350 more than thrombolytic administration. Recently, prospective cost-utility analysis from CADILLAC found no significant difference in 1-year aggregate costs between PCI with or without stent ($18,859 vs $18,690, p = 0.75)[27].

Conclusions

PCI with stenting has become the standard of care for acute myocardial infarction < 12 hours from symptom onset. This has led to decreased morbidity and mortality both short and long term compared to thrombolytic therapy. Antiplatelet glycoprotein IIb/IIIa inhibitors may have a role in improving TIMI flow prior to PCI and decreasing morbidity and mortality. The role of thrombolytics vs IIb/IIIa inhibitors in "facilitated reperfusion" is unclear at this time and further research is needed to define the indication of adjunctive pharmacology.

Riassunto

Diversi studi clinici randomizzati hanno dimostrato la superiorità, in termini di mortalità e morbilità, dell'angioplastica primaria sulla terapia fibrinolitica in pazienti con infarto miocardico acuto.

In una metanalisi di 22 trial randomizzati che includeva 50 246 pazienti, la trombolisi eseguita entro 2 ore dall'insorgenza dei sintomi apportava una riduzione in termini di mortalità quando confrontata con un trattamento più tardivo, mentre perdeva efficacia se somministrata dopo 6 ore dall'insorgenza dei sintomi. Di contro, è stato ormai largamente dimostrato che l'angioplastica può essere vantaggiosa sino a 12 ore dall'insorgenza dei sintomi, estendendo notevolmente la finestra terapeutica rispetto alla fibrinolisi nei pazienti con infarto miocardico acuto.

Nelle procedure di angioplastica primaria l'impianto di stent ha apportato consistenti vantaggi con una riduzione significativa delle percentuali di restenosi, eventi cardiovascolari avversi e riospedalizzazione in confronto alla semplice angioplastica. I trial FRESCO, PASTA, Stent-PAMI e CADILLAC hanno documentato una significativa riduzione di eventi, di restenosi e riocclusioni nel gruppo di pazienti sottoposti a procedura di angioplastica con stent rispetto a quelli senza stent.

Non sono ancora disponibili in letteratura chiari dati sull'utilizzo di stent medicati in corso di infarto miocardico acuto, anche se i risultati preliminari del trial SIRIUS suggeriscono che gli stent rivestiti di sirolimus possono ridurre significativamente l'incidenza di restenosi.

È ormai chiaro che l'uso di inibitori recettoriali delle glicoproteine piastriniche IIb/IIIa in corso di angioplastica primaria possa apportare vantaggi sulla riperfusione e sulla mortalità. Una metanalisi dell'ADMIRAL, del CADILLAC e di altri 10 studi condotti su 20 186 pazienti con infarto miocardico acuto sottoposti a procedure interventistiche, ha dimostrato che gli inibitori IIb/IIIa possono apportare una riduzione significativa di mortalità già a 30 giorni ($p = 0.024$).

In conclusione, l'angioplastica primaria costituisce oggi lo *standard of care* per i pazienti con infarto miocardico acuto che si presentano entro 12 ore dall'insorgenza dei sintomi, aumentando significativamente la sopravvivenza a breve e lungo termine, riducendo le complicanze intraospedaliere e le riospedalizzazioni, con notevoli vantaggi anche in termini di spesa sanitaria. Altre ricerche sono necessarie per definire quale sia il ruolo di terapie farmacologiche aggiuntive all'angioplastica primaria, in particolare dei trombolitici e degli inibitori IIb/IIIa o della loro terapia combinata, nella strategia della "riperfusione facilitata".

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