

Pharmacological Reperfusion in Acute Myocardial Infarction after ASSENT 3 and GUSTO V [81]

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Reperusão Farmacológica no Enfarte Agudo do Miocárdio Depois do ASSENT 3 e GUSTO V

Palavras-Chave

Enfarte agudo do miocárdio; Fibrinólise; Terapêutica antitrombótica

Key words

Acute myocardial infarction; Fibrinolysis; Antithrombotic therapy

The restoration of coronary flow after an acute myocardial infarction (AMI) has been the most remarkable advance in the treatment of acute coronary syndromes in recent decades.

Pharmacological and mechanical ways of achieving rapid and complete reperfusion of epicardial arteries have been the goal of many clinical trials.

Questions such as whether PCI is superior to fibrinolysis, or if bolus lytics are superior to perfusion drugs, or which is the best regimen of adjunctive therapy to fibrinolysis, have been extensively addressed.

Thrombolytic agents have become the cornerstone of pharmacologic treatment for acute myocardial infarction. However, the current agents are far from perfect. New thrombolytic drugs have been designed to overcome some of the shortcomings of the old drugs.

Development of these agents has focused not only on increasing plasma half-life, and thus allowing single-bolus administration, but also on improving fibrin specificity and resistance to plasminogen activator inhibitor. The safety and efficacy of several of these promising thrombolytic drugs have been evaluated in large-scale trials.

The two most recent large scale clinical trials on fibrinolysis for AMI (ASSENT 3 and GUSTO V)^(1, 2) have addressed some of the burning questions:

– Are bolus lytics equivalent (in terms of

efficacy and safety) to perfusion lytics?

- Can enoxaparin replace unfractionated heparin (UFH) as adjunctive antithrombotic therapy for fibrinolysis?
- Does the regimen with association of a lytic drug with abxiximab (an IIb/IIIa glycoprotein inhibitor) confer equal efficacy with better safety?

Trial designs and endpoints

The primary hypothesis of GUSTO V was that a IIb/IIIa antagonist with reduced-dose fibrinolytic therapy for emergency treatment of STEMI would improve clinical outcomes with equal or superior safety as compared with conventional thrombolysis. The primary end point was all-cause mortality at 30 days, and secondary end points included clinical safety and adverse events at 30 days. GUSTO V enrolled 16,588 patients who were in the first 6 hours of an evolving STEMI. Patients were randomly assigned to a standard-dose r-PA arm (n=8,260), or a halfdose r-PA with full-dose abxiximab arm (n=8,328)⁽²⁾.

The ASSENT-3 trial⁽¹⁾ was designed to evaluate LMWH, abxiximab and TNK in the treatment of STEMI. Six thousand patients were involved in the blinded, three-arm study that compared TNK plus unfractionated heparin (UFH) (n=2,038), half-dose TNK plus abxiximab and UFH (n=2,017), and TNK plus

LMWH (enoxaparin) (n=2,040). The composite efficacy end points of ASSENT-3 were reported in two sets: efficacy, and safety/efficacy. The arms that include enoxaparin and abciximab versus UFH are reported together and cannot be evaluated individually, but trend together.

Trial Main Results

In the GUSTO V trial⁽²⁾, at 30 days, 5.9% of the patients in the r-PA group had died compared with 5.6% of patients in the combined r-PA/abciximab group (p=0.43; 95% CI=0.83-1.08). The combined outcome of deaths or nonfatal reinfarction was less common in the combination group than with r-PA alone, and there was less need for urgent revascularization and fewer nonfatal ischemic complications of AMI. Although rates of ICH (0.6%) and nonfatal disabling stroke (0.9%) were similar between the two groups, there were more non-intracranial bleeding complications in the combination therapy group.

While the combination of r-PA/abciximab showed the same 30-day mortality as r-PA alone, there were significant improvements in several secondary end points. From an efficacy perspective, there was a lower need for PCI within the first week in the combination group (25.4%) compared with r-PA alone (27.9%) (p=0.008). Rates for coronary artery bypass graft were 3% for r-PA alone versus 3.7% for combination therapy (p=0.013). Furthermore, the combined end point of death and nonfatal reinfarction was lower with combination therapy (7.4%) than with r-PA alone (8.8%) (p=0.0011)⁽²⁾.

With regard to ICH, there was no difference between the groups (p=0.27) if the patients were younger than 75 years old. However, when a patient was older than 75, there was a significant interaction for ICH (p=0.033)⁽²⁾. Combination therapy is not recommended in this cohort, therefore this is a post-hoc non-prespecified analysis.

Similar to GUSTO V, the ASSENT III group which was treated with a combination of half-dose TNK and abciximab demonstrated a reduction in the efficacy endpoint compared to standard-dose TNK and heparin (11.1% versus 15.4%, p=0.0001)⁽¹⁾. Reinfarction was significantly reduced with the combination arm (2.2% versus 4.2%, p=0.0009), and refractory ischemia was significantly reduced as well (3.2% versus 6.5%, p=0.0001).

Non-intracranial bleeding, however, was increased in the combination arm (4.3%

versus 2.2%, p=0.0005). Intracranial bleeding was similar between the combination arm (0.9%) and the control group (p=0.98). These results mirror the results of GUSTO V, adding credibility to the argument that the addition of a IIb/IIIa agent to half-dose fibrinolytics has advantages beyond mortality reduction alone. Reinfarction and refractory ischemia are significantly reduced with the addition of a IIb/IIIa agent.

Some lessons can be taken from these two (and from previous) trials and are addressed in this article.

Lesson #1

Bolus fibrinolytics overtake accelerated tPA as standard drug for lytic therapy

Previous studies had demonstrated that “bolus lytics” were “non inferior” as compared with accelerated-tPA but they have indeed failed to demonstrate superiority^(3,4).

This notion was already incorporated into both the ASSENT 3 and GUSTO V trials, where bolus drugs were used, suggesting that these more fibrin specific drugs have come to stay in terms of fibrinolytic therapy for AMI.

If the bolus drugs are not better, not safer and not cheaper, then the main reason for changing from the conventional gold-standard drugs (like SK or alteplase) to the new drugs (reteplase or tenecteplase) must be because they are easier to use, allowing for significant reductions in nursing time and the need for perfusion systems.

Lesson #2

Bolus lytics allow for significant reductions in dosing errors

Some third-generation fibrinolytics may help reduce medical errors in administering medications.

Simplicity of the administration regimen and weight adjustment are just two of the aspects related to the more frequent errors.

Data from several large-scale trials indicate that, the more complicated the fibrinolytic regimen, the higher the likelihood of medication error, which is associated with increased mortality⁽⁵⁾.

The other aspect of safe lytic administration is weight-based dosing. In the ASSENT-2 trial, only 53% of patients were weighed⁽⁴⁾. When the patients in ASSENT-2 who were not weighed are analyzed, mortality triples. FDA post-hoc analysis of the ASSENT-1 and ASSENT-2

trials showed that patients with estimated weights who received weight-adjusted drugs had higher morbidity and mortality than patients with accurate weights. The outcome differences may be the result of the inability to obtain a weight in the critically ill patient, rather than a treatment effect.

A dosing error is probably even more important in smaller patients, where dose-weight discrepancies have a greater impact in terms of percentage. The National Registry of Medical Infarction (NRMI) registry showed that patients receiving >1.5 mg/kg t-PA have 1.2 to 2 times the risk of ICH⁽⁵⁾.

A bolus administration regimen can reduce errors and increase the safety and effectiveness of treatment. This is important, since the therapeutic window for fibrinolytic therapy is small and the potential for adverse outcomes from errors is high. This is particularly a concern in EDs whose staff does not routinely treat a large volume of patients with high-risk AMI. Bolus-dose therapy that does not require a patient's weight to be obtained is more convenient and may also be safer.

Lesson #3

GUSTO V and ASSENT 3 did not shorten time to treatment

Despite the fact that bolus drugs were used in both trials, the median time between first symptoms and first study drug was not significantly different from previous lytic studies. The median time to treatment was 2.7h in both ASSENT 3 and GUSTO V, compared with 2.8h in GUSTO I that was performed between 1990 and 1993⁽⁶⁾.

We can conclude that bolus treatment may be easier to use but this did not result in shorter time to treatment. The time spent by the patient to get help, together with the time spent by doctors to make the decision to start treatment, did not change significantly over the last decade.

Significant reductions in time to treatment could only be achieved by taking the reperfusion treatment to the pre-hospital environment, as shown in the recent ASSENT 3 PLUS trial, where the median time to treatment was reduced to 115 min⁽⁷⁾. The ease of use of bolus drugs makes them the preferable choice for out-of-hospital lytic treatment.

Lesson #4

Lowest 30-day mortality ever achieved in lytic trials

For the first time in in-hospital lytic trials, the 30-day mortality was reduced to less than 6% in both trials and in several arms.

Mortality at 30 days was reduced from 7.4% to 5.9% in patients receiving reteplase and UHF from GUSTO III to GUSTO V^(3, 2). Similar results were shown from ASSENT 2 to ASSENT 3 in patients receiving TNK-tPA and UHF with 30-day mortality being reduced from 6.17% to 6.0%, respectively^(4, 1).

One of the possible explanations for these results is that the more recent trials had relatively low risk populations. Indeed, there was a lower rate of anterior MIs, patients with a single elevated blood pressure were excluded in GUSTO V and there were fewer patients with previous MI in ASSENT 3, than in previous trials.

Lesson #5

Early patency did not translate into lower mortality

Pilot studies with the combination of half-dose lytics and abxiximab (like SPEED and TIMI 14 trials)^(8, 9) raised the hypothesis that better patency could result in significantly lower mortality rates in clinical practice.

The large RCTs analyzed here, however, did not show lower mortality of the combination as compared with conventional lytic therapy.

These results come as no surprise if a closer and deeper interpretation of the results of previous trials is made.

Back in the GUSTO I trial, a 20% improvement in TIMI 3 flow was needed to yield a 1% mortality reduction⁽¹⁰⁾.

In the dose-confirmation phase (core laboratory assessment) of the SPEED trial (considered as a pilot trial for the GUSTO V), there was a 7% improvement in the rate of TIMI grade 3 flow⁽⁸⁾. Therefore, if a 20% improvement is required to improve mortality by 1%, then a 7% improvement would be predicted to improve mortality by 0.3%. And that was exactly what was found in the GUSTO V (a 0.29% absolute reduction in 30-day mortality for the combination therapy)⁽²⁾.

These results led to the idea that trying to further improve reperfusion with drugs is probably not worthwhile. Future management of MI could consist of treatment with a fibrinolytic or with combination therapy, followed by immediate angioplasty.

However, to the question “could the combination therapy facilitate early PCI?” we have to reply: “Answer not yet given!”.

Although no excess bleeding was reported among patients undergoing PCI, in these two trials, the power of this analysis is limited given the small sample sizes.

Patients were not randomized to PCI vs no PCI and substudy analyses such as this are potentially biased.

Future large scale randomized trials are needed to address the efficacy of the facilitated PCI strategy.

GUSTO V and ASSENT 3 did not provide supportive data for this strategy.

Lesson #6

Abxiciimab use allowed half-dose lytic therapy with noninferior efficacy and with no increase of hemorrhagic risk

No differences were found in primary endpoints, in both studies, between combination and conventional lytic therapy.

The feared increase of severe hemorrhagic complications (namely of intracranial haemorrhage) with the combination therapy was not confirmed.

Lesson #7

Some subgroups seemed to benefit more from the combination therapy

Despite its risks and limitations, subgroup analysis showed some subgroups in which the combination of abxiciimab and lytics appeared more beneficial.

- * Patients aged less than 75 years in both trials
- * Patients with anterior MI in GUSTO V
- * Patients treated after 4h in GUSTO V and less than 4h in ASSENT 3

Lesson #8

Some subgroups did worse with the combination therapy

On the other hand, subgroup analysis also showed some subgroups in which this combination appeared more detrimental.

- * Patients older than 75 years in both trials
- * Diabetics in ASSENT 3

This analysis led to the next conclusion:

Lesson #9

The combination arm was harmful to the elderly in both GUSTO V and ASSENT 3

At this stage, we should recommend against combined abxiciimab and fibrinolytic in the elderly.

Caution should also be exercised when dealing with diabetics.

Should we be studying direct PCI or some facilitated approach for the elderly?

Lesson #10

Benefit was due to lower incidence of ischemic events

Although mortality did not show significant differences between treatments arms, both the combination of abxiciimab + lytics and enoxaparin + lytics showed fewer ischemic events during in-hospital stay.

Significant reductions were found in the incidence of in-hospital reinfarction in both trials, of recurrent ischemia in GUSTO V and of refractory ischemia in ASSENT 3.

Lesson #11

Benefit was shown in most of the prespecified MI complications

Although subgroup analysis could carry large biases, benefit was clear for many common MI complications in both trials.

This fact could have major positive implications in terms of AMI morbidity.

Lesson #12

Enoxaparin can replace UFHeparin as adjunctive therapy for fibrinolysis

Results of the enoxaparin arm of the ASSENT 3 trial showed that this LMWH is at least as efficacious and safe as UFH, and probably better.

These results were found in both the efficacy and efficacy+safety endpoints

Despite the good design and power of these two large randomized trials, there remain several unanswered questions:

Regarding the association of LMWH and fibrinolytics:

Are the results found with enoxaparin due to a class effect of LMWHs?

Is enoxaparin a desirable anticoagulant in conjunction with less fibrin-specific agents? Answers to this question will be given by the ongoing EXTRACT-TIMI 25 trial, in which enoxaparin and UFH are being compared in a double-blind manner in the context of

fibrinolysis for AMI.

Regarding the combination of IIB/IIIa inhibitors and fibrinolytics:

Can these data be extrapolated to other combinations of drugs?

What role will various pharmacologic combinations ultimately have in conjunction with early PCI?

Is this therapy cost-effective?

In summary:

PCI is the treatment of choice for STEMI. However, many hospitals are unable to provide this strategy on a 24 hours per day/7 days per week basis. In a situation where PCI is unavailable, other considerations may take precedence. First, in patients identified by EMS as having a STEMI, prehospital lytics may be considered, as this significantly decreases the time to therapy. Another option is directly transporting patients to a facility where PCI is available. In patients less than 75 years of age who are identified as having STEMI in a hospital that is unable to perform early PCI, lytic or combination therapy may be considered. In those older than 75 and unable to receive early PCI, fibrinolytic therapy is indicated. Finally, facilitated PCI may be considered, in those centers where PCI is readily available, after discussion with the local interventional cardiology team.

This guideline addresses procedural and practical issues raised in the ED and prehospital setting, as the standard of care for high-risk AMI moves toward combination therapy using IIB/IIIa inhibitors plus fibrinolytics and/or LMWH.

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