Review

The Use of Low Molecular Weight Heparins and Platelet GP IIb/IIIa Inhibitors as Adjuncts to Thrombolysis: Are there any Perspectives?

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The primary goal of therapy in acute ST-elevation myocardial infarction (AMI) is the restoration of coronary blood flow, by using either fibrinolysis or primary percutaneous coronary angioplasty (PTCA).[1,2] The pathophysiologic mechanisms involved in the acute coronary syndrome include plaque rupture, platelet aggregation and thrombosis.[3] The latter is promoted by enhanced thrombin activity after AMI.[4] On the other hand, an important paradox associated with the use of fibrinolytic therapy is its procoagulant potential, mainly through the release of a pool of trapped thrombin during the course of clot lysis.[4-6] However, conflicting data exist concerning the capacity of fibrinolytic agents to activate platelets directly.[4,7] Regardless of the controversial evidence on this subject, exposure of the clot-bound thrombin during fibrinolysis is an extremely potent platelet agonist, promoting platelet activation and aggregation.[8] Consequently, the above mentioned hypercoagulative state associated with AMI itself, as well as the procoagulant effect of fibrinolytic agents (the "thrombolytic paradox"), make the use of adjunctive antithrombin and antiplatelet therapies absolutely mandatory for the achievement of satisfactory and permanent myocardial reperfusion.[8]

Antithrombotic treatment

Unfractionated heparin (UFH) has been a standard treatment in the acute management of acute coronary syndromes (ACS with or without ST-elevation) for many years, providing a considerable reduction of the risk of recurrent ischemia.[9,10] However, UFH exerts its anticoagulant effect (inhibition of thrombin production) indirectly, requiring antithrombin III as a cofactor, while it is only effective against circulating and not clot-bound thrombin.[11]

Additionally, UFH is characterized by an unpredictable anticoagulant response, causing difficulties in maintaining therapeutic plasma levels and requiring frequent measurements of the APTT. Furthermore, there is a "heparin rebound" phenomenon, due to the reactivation of thrombotic process following treatment discontinuation. Additional disadvantages of UFH consist of neutralization by protein binding and activated platelets, hemorrhagic complications and potential risk of thrombocytopenia and osteoporosis.[9,11,13]

Therefore, the development of low molecular weight heparins (LMWH) has been motivated by the need to improve some of the pharmacologic and pharmacokinetic profiles of UFH. LMWH offer

a more predictable bioavailability, together with a higher anti-factor Xa:IIa ratio. This ratio depends on the kind of LMWH used and it is significantly higher for enoxaparin (3:1 versus 1:1 for UFH), resulting in a more powerful prevention of thrombin production and suppression of the coagulation positive feedback mechanisms. Furthermore, the advantages of LMWH over UFH extend to practical benefits: administration in two fixed subcutaneous doses, without the need for continual coagulation monitoring, represents a significant reduction in nursing time and laboratory costs.[9,12,13] Among the several representatives of LMWH, enoxaparin has also shown cost-effectiveness when compared to UFH in the treatment of unstable angina/non-Q AMI. Nevertheless, it should be noted that while enoxaparin has shown superiority over UFH with regard to clinical outcome,[14] other LMWH show equivalence.[15] This difference has been partly attributed to the very high level of anti-Xa relative to anti-IIa activity achieved with enoxaparin and to structural differences between each individual LMWH.[9] However, there are very few studies providing a direct comparison between different LMWH in the treatment of non-ST-elevation ACS. Quite recently, the EVET trial compared enoxaparin (1 mg/kg twice daily for as long as 7 days) with tinzaparin (175 IU/kg once daily for up to 7 days). The results of this trial were in favor of enoxaparin, regarding the composite endpoint of mortality and ischemic complications at days 7 and 30, while the rates of bleeding complications were similar in the two groups.[16]

Nevertheless, despite the encouraging findings regarding the superiority of LMWH, which has led to their extensive use in the treatment of non-ST-elevation ACS (unstable angina and non-Q wave AMI), relatively few studies have investigated the use of LMWH as antithrombotic adjuncts to thrombolysis in ST-elevation ACS. On the other hand, UFH in combination with fibrin-selective fibrinolytic therapy for AMI has been shown to improve early patency rates of the infarct-related artery,[6,9,17] though without any clear clinical benefits as far as mortality or recurrent ischemia are concerned.[18,19] Furthermore, trials such as TAMI-3 did not demonstrate any improvement in the early patency rates when UFH was added to standard fibrinolytic treatment with tpa (tissue plasminogen activator).[20] It should also be pointed out that there is a lack of large randomized trials demonstrating favorable clinical effects of the UFH and tpa combination. However, favorable data provided by a number of angiographic trials,[18,19] together with the short plasma elimination half life of UFH and the weak systemic fibrinolytic action of tpa, provide a rational base for the administration of UFH for 48 hours after thrombolysis with tpa.[21]

LMWH were first used in combination with streptokinase (SK) in relatively small clinical trials. The combination of enoxaparin with SK was associated by Glick et al, in a small study, with a significantly reduced rate of reinfarction and recurrent angina compared with standard UFH as adjunctive agent.[22] Later, two clinical trials (FRAMI-BIOMACS II) tested dalteparin versus placebo as adjuncts to SK and showed reduced echocardiographic evidence of left ventricular thrombus and less recurrent ischemia, but at the cost of more hemorrhagic complications.[23,24]

The HART II trial (Second trial of Heparins and Aspirin Reperfusion Therapy, 400 patients included) was actually the first randomized comparative angiographic study designed to clarify the potential role of enoxaparin, as an alternative adjunct to thrombolysis with tpa, in the emergency treatment of AMI. Although the primary objective of the trial was to demonstrate non-inferiority of enoxaparin, patency rates of the infarct-related artery 90 minutes after treatment approached the criterion of superiority in favor of enoxaparin (TIMI flow grades 2 and 3 found in 80.1% of patients in the enoxaparin group vs. 75.1% in the UFH group, p=NS). On the other hand, the rate of reocclusion from TIMI grade 3 flow to grade 0 or 1, was significantly lower in the enoxaparin group (1.3% vs. 11.0% for UFH, p=0.02). When the two groups were compared with respect to safety endpoints, they were found to be similar: in-hospital mortality rates were 4% in the enoxaparin group versus 4.5% in the UFH group, and mortality rates at 30 days were 4.5% and 5% respectively. Intracranial hemorrhage (ICH) occurred in 1% of patients in both groups. In-hospital non-intracranial major hemorrhage was found in 3.6% of patients receiving enoxaparin, vs. 3% in the UFH group (p=NS). Generally, there was not any statistically significant difference between the two groups as far as adverse events were concerned.[13]

Another large, randomized clinical trial providing evidence to support the use of LMWH as adjunctive therapy to fibrinolysis was the ASSENT-3 trial, designed to compare the efficacy and safety of 3 therapeutic regimens:

1. Tenecteplase (TNK) full-dose (30 mg if bodyweight was <60 kg, 35 mg if it was 60-69 kg, 40

Table 1. ASSENT-3 main results.

ENDPOINTS	Enoxaparin (n=2040)	Abciximab (n=2017)	UFH (n=2038)	p*
30-day mortality, in-hospital reinfarction or recurrent ischemia	11.4%	11.1%	15.4%	0.0001
30-day mortality, in-hospital reinfarction or recurrent ischemia, ICH or other (non-ICH) major hemorrhage	13.8%	14.2%	17.0%	0.0081
30-day mortality	5.4%	6.6%	6.0%	0.25
In-hospital reinfarction	2.7%	2.2%	4.2%	0.0009
In-hospital recurrent ischemia	4.6%	3.2%	6.5%	<0.0001
ICH	0.9%	0.9%	0.9%	0.98
Major hemorrhage (other than ICH)	3.0%	4.3%	2.2%	0.0005

* The levels of statistical significance mentioned above refer to the comparison between enoxaparin and UFH groups or between UFH and abciximab groups.

mg if it was 70-79 kg, 45 mg if it was 80-89 kg and 50 mg if it was 90 kg or more) plus enoxaparin (30 mg bolus IV before TNK administration, immediately followed by 1 mg/kg subcutaneously every 12 hours up to hospital discharge or revascularization and for a maximum of 7 days).

2. TNK full-dose plus weight-adjusted intravenous UFH for 48 h (60 U/kg bolus, maximum 4000 U before TNK administration, followed by an initial infusion of 12 U/kg/h, max 1000 U/h. The first blood sample for APTT assessment was drawn after 3 h and the dose was adjusted to maintain an APTT of 50-70 s).
3. TNK half-dose (15-25 mg, according to bodyweight) plus abciximab (Reo-pro) at a dose of 0.25 mg/kg bolus IV, followed by 0.125 μg/kg/min continuous infusion (maximum 10 μg/min) for 12 h. Because abciximab has an anticoagulant effect, a lower dose of UFH was given (40 U/kg bolus, max 3000 U and 7U/kg infusion, max 800 U/h), in order to achieve APTT 50-70 s. The first APTT measurement took place after 3 h in this group as well.

All three aforementioned groups were given aspirin 150-325 mg.

The results of the ASSENT-3 trial are summarized in table 1. Clearly, the enoxaparin group showed statistically significant reductions in AMI ischemic complications, similar to those seen in the abciximab group, but more consistent. Importantly, no increase in intracranial hemorrhage rate, no excess in thrombocytopenia, and only a modest but non-significant increase in major bleeding complications was seen, attributed mainly to the longer period of therapy with enoxaparin (7 days vs. 2 days in the UFH group).[25,26]

Recently, the results of the angiographic ENTIRE-TIMI 23 trial, similar in design to ASSENT-3, came to provide further support for the combination of enoxaparin with full-dose TNK, which was associated with similar TIMI 3 flow rates as UFH at an early time point (60 min), while exhibiting advantages over UFH with respect to ischemic events through 30 days (4.4% vs. 15.9%, $p=0.0005$). These findings were achieved with a similar risk of major hemorrhage in the two study groups (1.9% vs. 2.4%, respectively, $p=$NS).[27]

In addition, the results of the AMI-SK trial came to support the superiority of enoxaparin versus placebo as an adjunct to streptokinase, a non-fibrin-selective fibrinolytic agent. The enoxaparin group demonstrated higher rates of ST-segment resolution, as well as better patency rates of the infarct-related artery after 5-10 days, thus implying more effective reperfusion. There was also a statistically significant reduction in the combined endpoint of 30-day mortality, reinfarction or recurrent angina, clearly attributable to lower rates of reocclusion.[28]

In contrast, data provided by the angiographic trial ASSENT-3 Plus (pre-hospital thrombolysis with

TNK, followed by administration of UFH or enoxaparin, according to the dose regimens used in ASSENT-3 study) were not in favor of the TNK-enoxaparin combination when compared with the TNK-UFH regimen, mainly as far as safety is concerned: enoxaparin demonstrated a trend (not reaching statistical significance, however) towards reduction of the composite endpoint of 30-day mortality and in-hospital ischemic complications, but at the cost of a significant increase in total stroke and ICH, particularly in patients >75 years of age. Therefore, it is possible that lower doses of enoxaparin need to be tested in elderly patients.[29] The comparative results of the main trials using the combination of fibrinolytics with LMWH are summarized in table 2.

In conclusion, in view of the present data (mainly provided by HART-II and ASSENT-3 trials) and the ease of administration, enoxaparin can be regarded as an attractive alternative to UFH as an adjunct to fibrin-specific agents, such as tpa or TNK.[6,9,13] However, it remains to be confirmed whether enoxaparin is cost-effective when combined with thrombolytic agents, through studies on large populations, while it should also be clarified whether lower doses would be preferable for the safety of elderly patients. Currently ongoing clinical trials might provide enough evidence in the near future supporting the replacement of UFH by LMWH in the treatment of AMI, as a superior antithrombotic adjunct to fibrinolysis. Nevertheless, the European Society of Cardiology's guidelines for the treatment of ST-elevation AMI,[30] as well as the equivalent guidelines from the AHA/ACC (last revised in 1999),[17] have not yet included the use of LMWH in combination with fibrinolytics and simply recommend the use of a more fully weight-adjusted dose of UFH, with earlier monitoring of APTT.

Antiplatelet therapy in ST-elevation AMI:

GP IIb/IIIa inhibitors

Fibrinolytic therapy has become the cornerstone in the early treatment of AMI. By promptly restoring antegrade perfusion, infarct size is limited, ventricular function is less compromised and mortality rates are lowered.[31,32] However, thrombolytic reperfusion regimens have several limitations.[32] Depending on the agent used, patency of the infarct-related artery is established within 90 minutes after the initiation of treatment in only 60% to 80% of patients. Full antegrade perfusion (TIMI grade 3 flow) is achieved in only 30% to 50% of patients.[32,33] Additionally, it has been observed that sustained, tissue-level reperfusion occurs in approximately one fourth of patients (no-reflow phenomenon) and that after initially successful thrombolysis about 5% to 10% of patients experience reocclusion of the culprit coronary artery.[32,33] Thrombin and platelets associated with the coronary thrombus are not specifically targeted by fibrinolytic agents, but rather have paradoxically increased activity. These components contribute to the tendency for vessel reocclusion.[31,34]

Thus, adjunctive therapy with antithrombins and antiplatelet agents is essential in the successful treatment of the coronary thrombus in ST-elevation AMI. Aspirin, although it acts synergistically with thrombolytics to reduce mortality and prevent reocclusion, is a relatively weak antiplatelet agent, which inhibits platelet activation by the cyclooxygenase pathway. However, platelet activation continues to occur through alternative pathways, while platelet aggregation occurs through only one pathway and requires the binding of fibrinogen or von Willebrand factor to the specific glycoprotein IIb/IIIa receptor on the platelet surface.[34-36]

It would therefore seem reasonable that a strategy which targets the final common pathway for platelet aggregation via the GP IIb/IIIa receptor would prevent the prothrombotic effects of platelets in AMI. Recent studies have examined the use of combinations of GP IIb/IIIa inhibitors and fibrinolytic agents in establishing superior reperfusion success in ST-elevation AMI.[36] Nevertheless, it is clear that these strategies increase the cost of reperfusion therapy and perhaps its bleeding complications too.[37] On the other hand, although it would be reasonable that improvement in angiographic results may also be translated into improved clinical outcomes, this issue has not yet been proved in completed clinical trials.[25,38]

In the early 1990s, many animal studies evaluated the safety and efficacy of the combination of GP IIb/IIIa inhibitors with fibrinolytics. Their results demonstrated a more rapid, more complete and more sustained coronary reperfusion, without any significant increase in bleeding complications.[39] These promising animal experiments prompted studies in human subjects. However, combination of GP IIb/IIIa antagonist therapy with the-non-fibrin-specific fibrinolytic SK has resulted in excessive hemorrhagic complications (about 10% even without heparin) and early termination of this strategy in two

Table 2. Comparative results of the main trials combining fibrinolytics with LMWH.

TRIAL	DESIGN	PATIENTS	FIBRINOLYTIC	LMWH	RESULT for LMWH (compared with UFH or placebo)
BIOMACS-II	Randomized, placebo-controlled	101	SK	Dalteparin (only 2 doses sc : 100 IU/kg before SK and 120 IU/kg 12 h after)	1. Favorable trend for TIMI 3 flow at 90 min 2. Favorable for reduction of is chemic episodes at 6-24 h
FRAMI	Randomized, double-blind, placebo-controlled	776	SK	Dalteparin (120 U/kg sc x2)	1. Favorable for reduction of left ventricular thrombi at 9 days 2. Negative for bleeding complications
HART-II	Multicenter, randomized, open-label phase II trial, comparing LMWH with UFH	400	tpa	Enoxaparin (30 mg bolus IV, then 1 mg/kg/12h, for at least 3 days)	1. Favorable trend for 90 min patency rates 2. Lower reocclusion rates at 5-7 days 3. Favorable trend for mortality 4. Similar safety
ASSENT3	Multicenter, randomized, open-label, comparing 3 groups of patients: 1. TNK+enoxaparin 2. TNK+UFH for 48 hours 3. ½ dose TNK + abciximab+UFH 48 h	6,095	TNK	Enoxaparin (30 mg bolus IV, then 1 mg/ kg/12h, max 7 days)	1. Favorable for ischemic complications and in-hospital mortality 2. Similar 30-day mortality 3. Similar rates of stroke, ICH, bleeding complications
ENTIRE-TIMI23	Multicenter, randomized, open-label, comparing 4 groups of patients: 1. TNK+enoxaparin 2. TNK+UFH for 48 h 3. ½ dose TNK + abciximab +UFH 48 h 4. ½ dose TNK + abciximab+ enoxaparin	483	TNK	Enoxaparin (30 mg bolus IV, then 1 mg/kg/12h for the TNK group and 0.3 – 0.75 mg/kg for the tnk+ abciximab group)	1. Favorable for ischemic complications at 30 days 2. Similar rates of major bleeding 3. Similar TIMI 3 flow rates at 60 min
AMI-SK	Randomized, double-blind, placebo-controlled	496	SK	Enoxaparin (30 mg bolus IV, then 1 mg/kg/12h for 3-8 days)	1. Favorable for ECG stabilization 2. Positive for 5-10 day patency rates 3. Positive for reduction in 30-day mortality and ischemic complications
ASSENT 3 PLUS	Randomized, using prehospital thrombolysis, comparing LMWH with UFH (48 h)	1,639	TNK	Enoxaparin (30 mg bolus IV, then 1 mg/ IV, then 1 mg/kg/12h, max 7 days)	1. Favorable trend for 30-day mortality and in-hospital ischemic complications 2. Unfavorable for stroke, especially ICH >75 years

Table 3. Combination therapy (with Full-dose Fibrinolysis) versus fibrinolysis alone.

TRIAL	Design	Patients	Fibrinolysis	GPIIb/IIIa inhibitor	Patency	ECG	Reinfarction/ Recurrent ischemia	Bleeding complications
SK+eptifibatide	Randomized, double-blind, angiographic placebo-controlled	181	SK	eptifibatide	Higher TIMI 2 and 3 flow rates			Significantly higher rates of bleeding complications
TAMI-8	Angiographic, pilot study, the first to be performed in human	60	tpa	abciximab	TIMI 2 and 3 flow: 92%, versus 56% with t-pa		Favorable trend for the combination therapy	Comparable rates, but more frequent CABG-related hemorrhage
IMPACT AMI	Randomized, angiographic, double-blind, placebo-controlled (in the second phase)	180	tpa	eptifibatide	TIMI 3 flow at 90 min: 66% vs. 33% with tpa	Resolution in 65 min, vs. 116 min with placebo	Similar rates	Similar rates
PARADIGM	Randomized, 3 phase trial, partially angiographic, placebo-controlled	353	SK or tpa	lamifiban	Similar 90-min TIMI-3 flow, due to the limited number of patients	More rapid and more sustained resolution	Similar rates	Significantly higher bleeding complication rates, independent of the fibrinolytic agent used, especially in the elderly, in women and diabetic patients

similar phase II studies using either abciximab (Reopro) or eptifibatide (Integrelin).[39,40]

In contrast, data support the combination of fibrin-specific fibrinolytics – such as tpa, reteplase (rpa), or TNK – with several GP IIb/IIIa inhibitors. Analysis of the results derived from several angiographic trials using full-dose fibrinolytic therapy, like TAMI-8, IMPACT-AMI and PARADIGM, suggest more rapid and complete reperfusion with the combination therapy in AMI.[41-43] The comparative results of these trials are described in table 3. On the other hand, despite the apparent improvements in TIMI grade 3 flow rates and some clinical parameters, such as ECG stabilization, recurrent ischemia and reinfarction, none of these trials was large enough to provide statistically significant conclusions regarding clinical endpoints.[36,41-43] Moreover, the increased bleeding complications that occurred in the aforementioned trials, along with in vitro evidence suggesting lower fibrinolytic dose requirements when GP IIb/IIIa inhibitors are used, prompted the next phase of angiographic studies, such as SPEED, TIMI-14 and INTRO-AMI, which adopted the use of half-dose fibrinolytic therapy with GP IIb/IIIa inhibitors (abciximab in the first 2 trials and eptifibatide in the third one). The patency rates observed in all three studies were significantly higher in the combination groups, without any particular increase in bleeding complications. The chart in figure 1 demonstrates the superiority of the various combination therapies used in the previous 3 studies in relation to the TIMI flow grade 3 observed in 60 min (primary efficacy endpoint).[46]

As far as safety endpoints are concerned, there was not any statistically significant increase in major hemorrhage in the combination therapy groups.

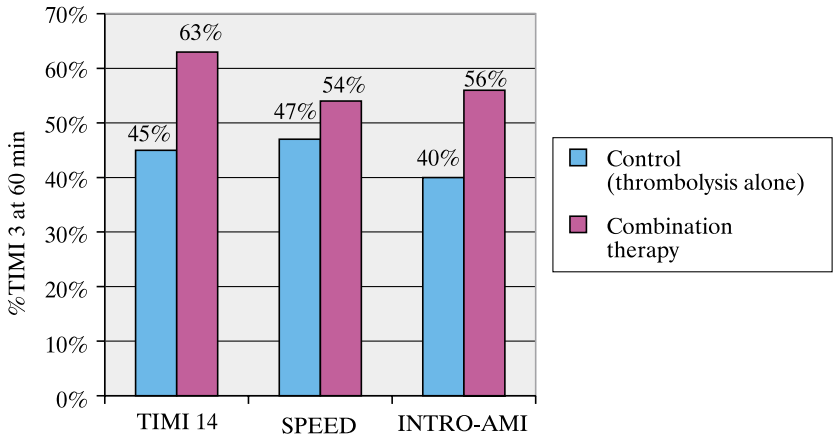

Figure 1. TIMI 3 flow rates at 60 min in the angiographic trials using combination therapy (thrombolysis + GPIIb/IIIa inhibitors) in ST-elevation AMI.

More precisely, the incidence of TIMI major bleeding was 7% in the combination of abciximab and tpa together with low-dose UFH in the TIMI 14 study (similar to that of standard thrombolytic therapy with tpa-UFH: 6%, p=NS).[34] In the SPEED trial, severe hemorrhage occurred in 9.8% of patients treated with the combination regimen (abciximab plus reteplase, p=NS when compared with rpa alone).[44,45] Finally, in the dose confirmation phase of the INTRO-AMI trial, the rate of TIMI major bleeding (by using eptifibatide in combination with tpa) was 8% in the low-dose eptifibatide group, 11% in the high-dose group and 6% in the full-dose tpa control group (p>0.05).[46] It should also be noted that the rate of major hemorrhage is generally higher in angiographic studies because of the mandatory instrumentation (about two thirds of the bleeding episodes occur at the catheterization access site). ICH occurred in 1%, 3% and 2% respectively in the above trials (p=NS when compared with fibrinolysis alone). Finally, mortality rates for the three groups were 4%, 5% and 7% and the incidence of reinfarction or need for percutaneous coronary intervention (PCI) at 30 days were also similar. Consequently, despite the mortality reduction expected when higher TIMI 3 flow rates are achieved (GUSTO I showed, however, that a 20% absolute increase in TIMI 3 flow needs to be obtained in order to achieve a 1% increment in survivorship with fibrinolysis),[21] these relatively small studies lacked the statistical power to estimate differences in clinical outcome or in the risk of infrequent complications like intracranial hemorrhage.[34,44-46]

Two more recent, but similar in design, angiographic trials are ENTIRE-TIMI23 (already mentioned in the discussion of LMWH)[27] and INTEGRITI.[47] The main results of all the trials that used combination therapy with half-dose fibrinolysis are summarized in table 4. Additionally, results of the ongoing FASTER study will be available in the near future, providing evidence about the efficacy and safety of the tirofiban/half-dose TNK combination, with ST-resolution at 60 and 90 min being the primary endpoint.

In order to provide a meaningful assessment of the combination therapy with fibrinolytics and GP IIb/IIIa inhibitors in the ST-elevation AMI, large-scale phase III clinical trials were necessary. GUSTO V was a powerfully designed trial, which enrolled 16,588 patients and estimated mortality differences between standard fibrinolytic treatment (reteplase at the standard dose of 10 U boluses, 30 min apart) and the combination of half-dose reteplase (two boluses of 5 U, 30 min apart) plus abciximab (0.25 mg/kg bolus and 0.125 μg/kg min infusion, max 10 μg/min, for 12 h). All patients received aspirin (150-325 mg) and UFH (5000 U bolus and 1000 U/h infusion in the rpa group, 60 U/kg bolus and 7 U/kg/h in the combination therapy group). Thirty-day mortality rate was the primary endpoint. Secondary endpoints included the composite of death and non-fatal disabling stroke, reinfarction, recurrent ischemia, urgent revascularization, ICH and non-intracranial bleeding complications, as well as one year mortality.[38]

All-cause mortality at 30 days was 5.9% for the reteplase group versus 5.6% for the combination group (p=0.45:NS). However, this 0.3% absolute decrease in mortality fulfilled the criteria of non-inferiority for the combination therapy. The lack of superior survival benefit at 30 days has been attributed, at least in part, to the unexpectedly low mortality rate

Table 4. Combination therapy (with half-dose fibrinolysis) versus fibrinolysis alone.

TRIAL	Design	Patients	Fibrinolytic agent	GPIIb/IIIa inhibitor	Patency	ECG	Reinfarction/ Recurrent ischemia	Bleeding Complications
TIMI - 14	Multi-center, randomized, angiographic, open-label phase II trial	888	SK or tpa	abciximab	Significantly higher TIMI 3 flow rates at 60 and 90 min	59% ST-resolution at 90 min vs. 37% with tpa ($p<0.0001$)	Similar rates	Similar rates for the tpa group. Higher rates in the SK-combination group
SPEED	Multi-center, randomized, angiographic, open-label	528	rpa	abciximab	Significantly higher TIMI 3 flow rates at 60 min		Similar rates	Similar rates
INTRO-AMI	Multi-center, randomized, angiographic, open-label	344	tpa	eptifibatide	Significantly higher TIMI 3 flow rates at 60	Similar rates of ECG-stabilization at 3 hours and 90 min	Similar rates	Similar rates
ENTIRE-TIMI23	Multi-center, randomized, angiographic, open-label	483	TNK	abciximab	Significantly higher TIMI 3 flow rates at 60 min	Significantly higher ST -resolution at 180 min (52-57% vs. 38-48%)	Lower rates of reinfarction	Trend towards more non-intracranial hemorrhage
INTEGRITI	Multi-center, randomized, angiographic, open-label	438	TNK	eptifibatide	Favorable trend for TIMI 3 flow at 60 min	Favorable trend for ST-resolution (71% vs. 61%)		Trend towards more non-intracranial hemorrhage and more transfusions
GUSTO V	Multi-center, randomized, clinical, open-label	16,588	rpa	abciximab			Significantly lower rates	Significantly higher rates of spontaneous non-intracranial hemorrhage, transfusions and thrombocytopenia
ASSENT 3	Multi-center, randomized, clinical, open-label, evaluating 3 regimens: 1.TNK+enoxaparin 2. TNK +UFH for 48 hours 3. ½ dose TNK + abciximab+UFH for 48 hours	6,095	TNK	abciximab		More rapid and complete ST-resolution in the TNK/ abciximab group ($p=0.026$)[49]	Significantly lower rates	Significantly higher rates of spontaneous non-intracranial hemorrhage, transfusions and thrombocytopenia

Table 5. Gusto V TRIAL- Efficacy Endpoints.

ENDPOINT	Reteplase (rpa)	rpa+abciximab	p
30-day mortality	5.9%	5.6%	0.45 (NS)
Death or non-fatal AMI	8.8%	7.4%	0.0011
Death, AMI, urgent PCI	20.6%	16.2%	<0.0001
Reinfarction	3.5%	2.3%	<0.0001
Urgent PCI at day 7	27.9%	25.4%	<0.0001

The AMI complications at day 7, as well as the rate of recurrent ischemia were also significantly lower in the combination therapy group (p<0.0001).

(5.9%) in the reteplase group, which represents the lowest mortality rate of any large trial of AMI. The results of the GUSTO V trial, regarding the main efficacy and safety endpoints, are described in table 5 and provide quite favorable data for the efficacy of combination therapy, particularly as far as early ischemic complications are concerned. Since the true benefit in mortality might only be realized at a later point, the 1-year follow up of survival could ultimately prove to be important. Nevertheless, all-cause mortality at 1-year follow-up has been shown to be similar in both groups (8.38% in both of them, $p>0.99$). Early reinfarction (within 7 days) was a factor powerfully correlated with higher 1-year mortality (22.6% vs. 8% in the subgroup without reinfarction, p<0.001).[48] However, even though this complication was rarer in the combination therapy group (2.3% vs. 3.5%), treatment assignment itself did not significantly influence mortality.[48] For the composite of death or non-fatal myocardial infarction, the rate was 8.8% in the reteplase group vs. 7.4% in the combination group, (p=0.0011), while for the composite of death, reinfarction or urgent PTCA the rate was 20.6% and 16.2% respectively (p<0.0001). On the other hand, as shown in table 6, there was no difference between the two groups in terms of non-fatal disabling stroke and ICH in particular. However, there was a significant (p=0.033) interaction of combination treatment by age (<75 or ≥75 years) for ICH. The rate of bleeding associated with coronary-artery bypass grafting or cardiac catheterization procedures was not higher in the combination group. In contrast, rates of spontaneous non-intracranial hemorrhage, predominantly from the gastrointestinal system, were significantly higher among those patients (p<0.0001) and so were the rates of blood transfusions and thrombocytopenia (p<0.0001).[38]

Another large clinical trial designed to assess differences in clinical outcome was ASSENT-3, which included 6,095 patients. This study has already been discussed in the LMWH part of the present article, where the dose regimens are described in detail. The primary efficacy endpoint was the composite of 30-day mortality and in-hospital reinfarction or recurrent ischemia. Statistical significance demonstrating efficacy superiority was reached by both the enoxa-

Table 6 Gusto V TRIAL- Safety Endpoints.

ENDPOINT	rpa	rpa+abciximab	p
Total stroke	0.9%	1.0%	0.55 (NS)
Intracranial hemorrhage (ICH)	0.6%	0.6%	0.79 (NS)
ICH>75 years old	1.1%	2.1%	0.069
Moderate-severe (non-intracranial) hemorrhage (catheterization-CABG)	0.4%	0.3%	0.355 (NS)
Spontaneous non-intracranial hemorrhage	1.9%	4.3%	<0.0001
Blood transfusions	3.7%	5.0%	<0.0001
PLT<10^5/mm^3	0.7%	2.9%	<0.0001

parin and abciximab groups, but the efficacy plus safety endpoint was reached only by the enoxaparin group.[25] Table 1 summarizes the results of the trial, concerning the efficacy and safety of the three regimens used, describing the main simple and composite endpoints. Results concerning the combination therapy group are also referred to in table 4.

It is obvious that the results obtained with half-dose TNK plus abciximab are very similar to those seen in GUSTO V with half-dose reteplase and abciximab and support the hypothesis that a more potent antiplatelet agent, which increases flow in the infarct-related coronary artery, reduces the frequency of ischemic complications of AMI, at the cost of a higher rate of non-intracranial bleeding complications. However, no benefit, and perhaps even harm, was seen in patients older than 75 years. Thirty-day mortality was not different among the 3 groups, while there are interesting data provided by the recently published 1-year follow-up in the subgroup of patients who underwent an urgent or elective PCI.[49] More precisely, there were no differences in mortality or clinical events for the patients who underwent an elective PCI. On the contrary, despite the fact that urgent PCI was necessary in significantly fewer patients of the abciximab and enoxaparin groups (9.1% and 11.9%, respectively, vs. 14.3% in the UFH group, $p<0.0001$), the outcome after the urgent PCI was less favorable in these patients: 30-day mortality rates were 8.2%, 5.4% and 4.5% respectively, while 1-year mortality rates were 11%, 8.5% and 5.6% ($p<0.045$ for abciximab vs. UFH). There were also more major bleeding complications (8.8%, 7% and 3.4% respectively, $p<0.012$ for abciximab vs. UFH), thus raising further hesitancy over the adoption of combination therapy in clinical practice.[49] The results of the aforementioned trials with half-dose fibrinolysis plus GP IIb/IIIa platelet inhibitors are summarized in table 4. Therefore, the favorable angiographic and clinical results obtained with the combination therapy, although not confirmed by differences in mortality, suggest that there might be a role for this treatment, especially in younger patients with ST-elevation AMI who are eligible candidates for coronary intervention. In particular, the SPEED angiographic trial has shown a significant improvement in the reperfusion rates achieved with pharmacologic combination therapy followed by early PCI ("facilitated" PCI, as opposed to "primary" PCI, which is not preceded by pharmacological treatment of the coronary thrombus).[25,36,38,44-46] It can therefore be concluded that GP IIb/IIIa platelet inhibitors may play a pivotal role in coronary reperfusion before, during and after the completion of early PCI. However, this needs further confirmation by large randomized trials designed to compare facilitated versus primary PCI in ST-elevation AMI. The PACT trial evaluated the efficacy and safety of facilitated PCI (half-dose tpa before the intervention) vs. primary PCI. The group of the facilitated PCI demonstrated higher TIMI 2 and 3 flow rates on angiography immediately before PCI, better left ventricular function preservation and no increase in stroke or major bleeding.[50] Additionally, ASSENT-4 PCI is an ongoing clinical trial, evaluating the efficacy and safety of TNK administration followed by PCI, versus PCI without pharmacologic pretreatment. Patients recruited in the study are AMI patients with an expected delay for the intervention >60 min. The study design was announced at the 2002 AHA Congress and the primary endpoint will be the composite of mortality, heart failure and cardiogenic shock at 90 days.

Nevertheless, at present there are insufficient data available to provide evidence for the standard use of combination therapy with fibrinolytics and GP IIb/ IIIa platelet inhibitors as a first-line treatment of ST-elevation AMI, especially in patients not eligible for PCI. However, a more extensive application of this strategy might be expected in future, in view of new data resulting from currently ongoing trials. On the other hand, as has already been mentioned, LMWH are much closer to the target of obtaining an important role as an adjunct to thrombolysis with fibrin-specific agents, contributing to our continual efforts for rapid, complete and sustained reperfusion.[25]

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