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Considerations in Combination Therapy: Fibrinolytics plus Glycoprotein IIb/IIIa Receptor Inhibitors in Acute Myocardial Infarction

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Summary: The combined use of a fibrinolytic and a platelet glycoprotein (GP) IIb/IIIa receptor inhibitor to target the fibrin and platelet components of occlusive thrombi offers the potential for more rapid and complete reperfusion in patients with acute myocardial infarction (MI), although there have been concerns about the safety of this combination therapy. Data from the recent GUSTO-V and the ASSENT-3 trials support the use of this regimen in that the 30-day death or nonfatal reinfarction rate (7 days) in GUSTO-V and death or in-hospital reinfarction or in-hospital refractory ischemia rate in ASSENT-3 were reduced ($p = 0.001$ and $p = 0.0001$, respectively). The need for revascularization in both these trials was also reduced significantly. There was no increased risk of intracranial hemorrhage or stroke with the combination therapy, but an increased rate of nonintracranial severe or major bleeding was observed. At present, patients aged > 75 years should not receive combination therapy. Further studies in subgroup patient populations are warranted.

Key words: glycoprotein IIb/IIIa receptor inhibitors, thrombolysis, heparin

Introduction

Thrombolytic therapy in patients with acute ST-elevation myocardial infarction (MI) substantially reduces short- and long-term mortality.[1–5] Numerous trials have demonstrated a significant effect of glycoprotein (GP) IIb/IIIa receptor inhibitors in reducing ischemic complications in patients receiving percutaneous coronary intervention (PCI).[6,7]

The combination of a fibrinolytic agent and a platelet inhibitor is a strategy motivated by the recognition that occlusive thrombi contain both fibrin-rich and platelet-rich components.[8,9] Furthermore, fibrinolysis exposes clot-bound thrombin, which increases platelet aggregation by activating GP IIb/IIIa receptors.

Pilot studies demonstrated improved reperfusion with combination therapy of thrombolytic and GP IIb/IIIa inhibitors compared with thrombolytic therapy,[10–12] however, differences were noted in the risk of major bleeding events among the combination regimens tested.

This article will review the clinical trials (phase II and III) that investigated the management of ST-elevation MI with the combination of fibrinolytic therapy and GP IIb/IIIa inhibitors.

Thrombolysis in Myocardial Infarction (TIMI)-14 Trial

The phase II TIMI-14 trial comprised two treatment arms in patients with ST-segment elevation MI (within 12 h): one evaluated the combination of alteplase or streptokinase with abciximab ($n = 888$)[13] and the other evaluated the combination of reteplase and abciximab ($n = 299$).[14]

In the first arm, patients were randomized to standard-dose alteplase or standard-dose abciximab bolus plus infusion alone or in combination with a range of doses of alteplase or streptokinase; the control patients received standard weight-adjusted heparin, whereas those receiving abciximab received low-dose heparin (60 U/kg bolus [maximum 4000 U] and 7 U/kg/h infusion [maximum 800 U/h]).[13] The most promising combination was the alteplase 50 mg (15 mg bolus; 35 mg infusion/60 min) plus abciximab (bolus 0.25 mg/kg; 12-h infusion: 0.125 µg/kg/min), along with low-dose or very-low-dose heparin (30 U/kg bolus; 4 U/kg/h infusion). Rates of TIMI grade 3 flow were significantly higher in the pooled combination group that received low-dose heparin than in the alteplase control group at both 60 and 90 min (Fig. 1).[13] In addition, rates of TIMI grade 3 flow were somewhat lower in the very-low-dose heparin group (69% at 90 min).

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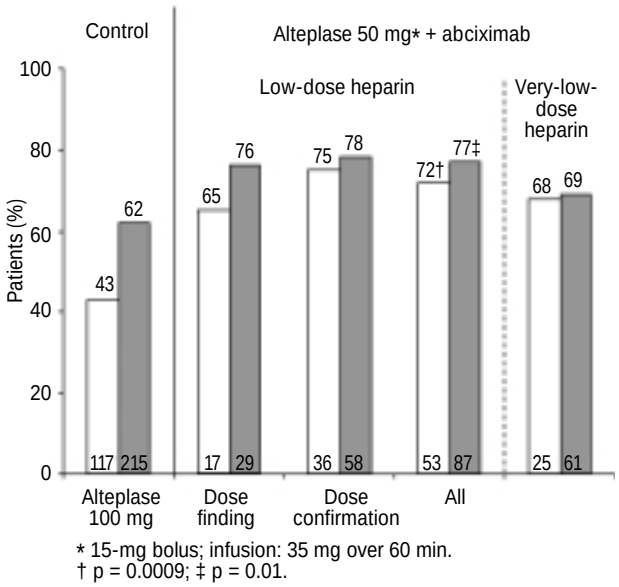

FIG. 1 Percent of patients achieving TIMI grade 3 flow at 60 (□) and 90 (■) min in the TIMI-14 trial. Adapted from Ref. No. 13 with permission.

The rate of major bleeding was 7% in the alteplase plus abciximab and low-dose heparin group and 1% in the alteplase plus abciximab and very-low-dose heparin group, compared with 6% in the alteplase control group, 3% in the abciximab-alone group, and 10% in all the streptokinase plus abciximab groups combined. Streptokinase combined with abciximab produced a dose-related increase in major hemorrhage. Similarly, for combination therapy with full-dose streptokinase and escalating eptifibatide doses, an increased risk of moderate/severe bleeding was observed.[15] It was suggested that this may be because of the increased systemic disturbances in the hemostatic system that occur with less fibrin-specific agents, such as streptokinase,[13] resulting in the discontinuation of combination therapy with streptokinase.

The overall rate of intracranial hemorrhage (ICH) was 1.1%, with no statistically significant differences observed between regimens. The authors concluded that the improvement in reperfusion with all the combined half-dose alteplase and abciximab groups was not associated with increased risk of bleeding.

In the second arm of TIMI-14, patients were randomized to standard-dose, double-bolus reteplase (10 U + 10 U) and standard weight-adjusted heparin or standard-dose abciximab plus reduced-dose reteplase with low-dose (60 U/kg bolus; 7 U/kg/h infusion) or very-low-dose (30 U/kg bolus; 4 U/kg/h infusion) heparin.[14] Rates of TIMI grade 3 flow at 90 min were 70% in the reteplase control group, 73% in the abciximab plus half-dose reteplase (5 U + 5 U) group, and 77% in the abciximab plus reteplase (10 U + 5 U) group. There were no differences in flow rates observed according to low-dose or very-low-dose heparin use.

The overall rate of ICH in this second arm of TIMI-14 was 1.3%, while the overall major bleeding rate was 6%. No significant differences between dosage groups were observed with regard to incidence of ICH. However, major bleeding was more common in the combination group that received reteplase 10 U + 5 U (12%; 14% in the low-dose heparin group and 10% in the very-low-dose heparin group) compared with the control group (4%) and the combination group that received reteplase 5 U + 5 U (4%; 2% in the low-dose heparin group and 5% in the very-low-dose heparin group). In total, ICH occurred in none of the control patients, in one patient who received the combination that included reteplase 5 U + 5 U, and in three patients who received the combination that included reteplase 10 U + 5 U.

Thus, the results of the TIMI-14 trial demonstrated that combination of half-dose fibrinolytic plus the GP IIb/IIIa receptor inhibitor abciximab enhanced the incidence and speed of reperfusion in patients presenting within 12 h of onset of MI symptoms. As both arms of TIMI 14 were dose ranging, the small numbers of patients were not adequate to assess safety satisfactorily.

Strategies for Patency Enhancement in the Emergency Department (SPEED)

The SPEED phase II trial comprised two treatment arms (phases A and B) and included patients with ST-segment elevation MI (< 12 h presentation).[16]

Patients in phase A (n = 304) were randomized to abciximab alone or abciximab with various single- or double-bolus reduced doses of reteplase. All received heparin (60 U/kg bolus; infusion titrated to activated clotting time of ≥ 200 s).

Phase B of the study compared abciximab plus reteplase 5 U + 5 U (best combination identified in phase A; heparin bolus: 40 U/kg, maximum 4000 U) with full-dose reteplase (10 U + 10 U) alone (heparin bolus: 70 U/kg, maximum 5000 U) in 224 patients. Thrombolysis in Myocardial Infarction grade 3 flow was observed in 54% of the combination treatment group compared with 47% of patients in the reteplase-alone group (p = 0.39). Patients from both phases showed a trend toward greater reperfusion with the combination regimen that used higher-dose compared with low-dose heparin.

The addition of abciximab to reteplase was associated with a trend toward increased major bleeding without significantly increasing the rate of transfusions.[16] In phase B, major bleeding occurred in 3.7% of the reteplase-alone group and 9.8% of the abciximab plus low-dose reteplase group. Intracranial hemorrhage occurred in 0.9% of patients who received reteplase alone and in none of the recipients of abciximab plus low-dose reteplase.

Taken together, the results from TIMI-14 and SPEED found that the highest rates at 60 min of TIMI grade 3 flow were achieved with standard-dose abciximab combined with half-dose alteplase or half-dose reteplase. Reaching TIMI grade 3 flow with these regimens also appeared to be sensitive to the amount of heparin administered. Both studies showed that the addition of lower-dose heparin (TIMI-14: 30 U/kg; SPEED: 40 U/kg) resulted in slightly lower rates of TIMI grade 3 flow.

Integrilin and Low-Dose Thrombolysis in Acute Myocardial Infarction (INTRO-AMI)

The INTRO-AMI study (phase II) evaluated two doses of tissue plasminogen activator (t-PA), 25 and 50 mg, in combination with single or variable double-bolus doses of eptifibatide in patients with ST-segment elevation MI presenting within 6 h of onset of symptoms.[17] In phase A (dose finding; 344 patients), the best rate of TIMI grade 3 flow was achieved using 180/90 µg/kg double bolus and 1.33 µg/kg/min eptifibatide infusion combined with 50 mg of t-PA (65 and 78% at 60 and 90 min, respectively). Phase B (dose confirmation; 305 patients) investigated eptifibatide 180/90 µg/kg double bolus with 1.33 or 2.0 µg/kg/min infusion and 50 mg t-PA versus weight-adjusted t-PA (maximum 100 mg). The 60-min TIMI grade 3 flow rates were 42, 56, and 40%, respectively, and at 90 min, 53, 62, and 54%, respectively.

The combination of t-PA and eptifibatide was not associated with a significant increase in the rate of major bleeding complications relative to those seen with t-PA therapy alone. Although the patient numbers were too small to assess significance, there was a suggestive increase in the rates of ICH.

Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT-3)

The ASSENT-3 trial investigated the use of the fibrinolytic tenecteplase (TNK) in combination with enoxaparin, abciximab, or unfractionated heparin in patients with ST-segment elevation MI who presented within 6 h of symptom onset.[18] Patients were randomly assigned to receive

- full-dose TNK plus enoxaparin (30 mg intravenously followed by 1 mg/kg twice daily, subcutaneously, for a maximum of 7 days; n = 2,040);
- half-dose TNK plus reduced-dose unfractionated heparin (40 U/kg bolus [maximum 3000 U] followed by 7 U/kg/h infusion [maximum 800 U/h] for up to 48 h) and abciximab (0.25 mg/kg bolus, followed by a 12-h infusion of 0.125 µg/kg/min) (n = 2,017); or
- full-dose TNK plus unfractionated heparin (60 U/kg [maximum 4000 U] followed by 12 U/kg/h infusion [maximum 1000 U/h] for a minimum of 48 h [activated partial thromboplastin time 5–70 s]) (n = 2,038).

All patients received aspirin (150–325 mg). The primary endpoints included one for efficacy (composite of mortality, in-hospital reinfarction, or in-hospital refractory ischemia at 30 days) and another for efficacy plus safety (the primary efficacy endpoint plus in-hospital ICH or in-hospital major bleeding other than ICH).

With regard to the 30-day primary efficacy endpoint, a significantly greater benefit was seen with both the full-dose TNK plus enoxaparin and the half-dose TNK plus abciximab and heparin regimens compared with full-dose TNK plus heparin (Fig. 2) (p = 0.0001). These benefits were noted at 48 h and continued to be documented during the duration of the study. The 30-day mortality rates were similar across the treatment groups. The abciximab-based combination regimen demonstrated significantly lower rates of in-hospital reinfarction (p = 0.0009) and a decreased need for urgent PCI (p < 0.0001) and intra-aortic balloon pump (p = 0.01) compared with the TNK-heparin combination.

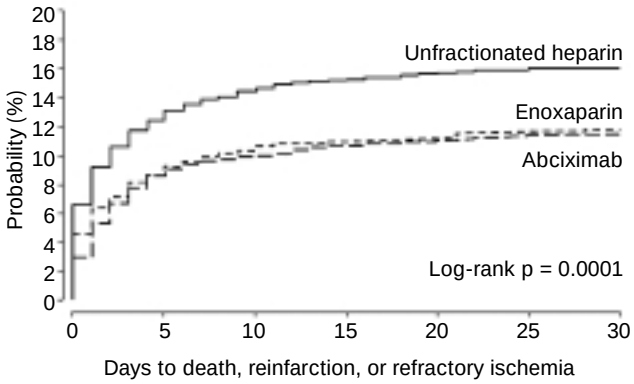

FIG. 2 Kaplan-Meier curves for the composite of 30-day mortality, in-hospital reinfarction, or in-hospital refractory ischemia in the ASSENT-3 trial. Adapted from Ref. No. 18 with permission.

The patient subgroup analysis of the primary efficacy and efficacy-plus-safety endpoints found that patients aged > 75 years or who had diabetes did not benefit from the abciximab-based regimen. Furthermore, major bleeding complications in elderly patients and those with diabetes who received abciximab were substantially higher than in those who received the TNK-heparin combination. Thus, although this trial was not powered to assess this endpoint in subgroups, older patients with MI or those with diabetes may require special considerations when this potent reperfusion strategy is planned.

Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO-V)

The GUSTO-V trial was the first large-scale, phase III trial designed to evaluate the use of the combination of GP IIb/IIIa receptor inhibition and reduced-dose fibrinolytic therapy in patients with ST-segment elevation MI presenting within 6 h of symptom onset.[19] A total of 16,588 patients were randomized to receive either standard-dose reteplase (n = 8,260) or abciximab (0.25 mg/kg bolus, followed by a 12-h infusion of 0.125 µg/kg/min) (n = 8,328) plus half-dose reteplase (5 U + 5 U). Adjunctive medications included aspirin and heparin (lower dose for the combination group).

The primary endpoint for this study was 30-day mortality, with secondary endpoints consisting of the composite of death and nonfatal disabling stroke, reinfarction, recurrent ischemia, urgent revascularization, ICH and non-ICH bleeding complications, and 1-year mortality.

The combination of abciximab and half-dose reteplase had no significant effect on the rate of all-cause mortality at 30 days compared with reteplase alone (Fig. 3): the rate of all-cause mortality in the combination therapy group was 5.6% compared with 5.9% in the reteplase-alone group (p = 0.43).

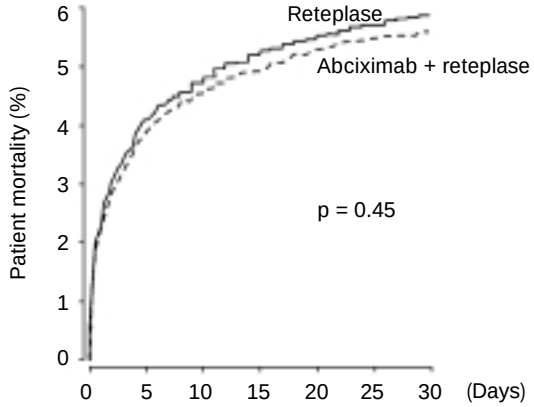

FIG. 3 Thirty-day mortality Kaplan-Meier curves from the GUSTO-V trial. Adapted from Ref. No. 19 with permission.

Patients treated with the combination of abciximab plus half-dose reteplase were 34% less likely to experience reinfarction than those treated with reteplase alone (2.3 vs. 3.5% of patients, respectively; $p < 0.0001$) (Table I). The combination regimen significantly reduced the need for PCI within 6 h of MI compared with reteplase alone (5.6 vs. 8.6% of patients, respectively; $p < 0.0001$). This benefit also was noted at 7 days for both PCI (25.4 vs. 27.9% of patients, respectively; $p < 0.0001$) and for coronary bypass surgery (3.0 vs. 3.7% of patients, respectively; $p = 0.013$). In addition, the 7-day or discharge composite endpoint of death, reinfarction, or urgent PCI was 21% less in the combination therapy group than the reteplase-alone group (16.2 vs. 20.6% of patients, respectively; $p < 0.0001$). At 30 days, the composite endpoint of death or nonfatal reinfarction was 16% less in patients who received the combination regimen compared with reteplase alone (7.4 vs. 8.8% of patients, respectively; $p = 0.0011$).

Both treatment regimens were not associated with an increase in nonfatal, disabling stroke and ICH (Table II). However, the use of either treatment regimen in patients aged > 75 years was associated with an increase in ICH compared with patients aged < 75 years ($p = 0.033$). In patients aged > 75 years, 2.1% who received the combination regimen and 1.1% who received reteplase alone experienced ICH ($p = 0.069$). Non-ICH bleeding ($p < 0.0001$), transfusion rates ($p < 0.0001$), and thrombocytopenia ($p < 0.0001$) were higher in the combination group, but procedure-related bleeding was similar in both groups ($p = 0.355$).

The authors concluded that although 30-day mortality was similar between the two treatment groups, the combination regimen produced significant improvement in a number of endpoints, including a decreased need for PCI or coronary artery bypass graft, less recurrent ischemia, and less reinfarction. The authors also noted that the results from GUSTO-V should be considered specific to the particular agents and doses used because of the pharmacologic differences among the various GP IIb/IIIa receptor inhibitors. Furthermore, the results from this study confirm that combination therapy with a fibrinolytic plus a platelet GP IIb/IIIa receptor inhibitor in patients with acute MI reduces reinfarction and revascularization rates without a concomitant increase in the incidence of ICH and nonfatal stroke. Although GUSTO-V found that combination therapy was associated with an increased rate of non-ICH, this can be effectively managed. Despite being in a high-risk

TABLE I Complications of myocardial infarction from the GUSTO-V trial

	% Patients	
	Abciximab + half-dose reteplase (n = 8,328)	Full-dose reteplase (n = 8,260)
Reinfarction at 7 days	2.3 [a]	3.5
Urgent PCI		
Within 6 h	5.6 [a]	8.6
At 7 days	25.4 [a]	27.9
CABG		
Within 6 h	0.1	0.1
At 7 days	3.0 [b]	3.7
Composite of death, reinfarction, or urgent PCI		
At 7 days or discharge	16.2 [a]	20.6

[a] $p < 0.0001$ versus full-dose reteplase.
[b] $p = 0.013$ versus full-dose reteplase.
Abbreviations: GUSTO-V = Global Use of Strategies to Open Occluded Coronary Arteries-V, PCI = percutaneous coronary intervention, CABG = coronary artery bypass graft.

TABLE II Major bleeding complications and nonfatal, disabling stroke in the GUSTO-V trial

	% Patients	
	Abciximab + half-dose reteplase (n = 8,328)	Full-dose reteplase (n = 8,260)
Nonfatal, disabling stroke (%)	20 (0.2)	26 (0.3)
ICH		
> 75 years (%)	24 (2.1)	12 (1.1)
≤ 75 years (%)	28 (0.4)	37 (0.5)
Severe bleeding (%)	90 (1.1) [a]	42 (0.5)
Moderate bleeding (%)	289 (3.5) [a]	148 (1.8)
Severe or moderate nonintracranial bleeding (%)	379 (4.6) [a]	190 (2.3)
Associated with CABG or PCI (%)	27 (0.3)	34 (0.4)
Spontaneous (%)	357 (4.3) [a]	160 (1.9)

[a] $p < 0.0001$ vs. full-dose reteplase.
Adapted with permission from The GUSTO-V Investigators.[19]
Abbreviations as in Table I.

subgroup, the use of combination therapy in the elderly and in patients with diabetes requires further investigation.

Enoxaparin and TNK-t-PA with or without GP IIb/IIIa Inhibitor as Reperfusion Strategy in ST-Elevation Myocardial Infarction (ENTIRE-TIMI 23)

This is an open-labelled study, evaluating patients presenting within 6 h of symptom onset who, after receiving aspirin, were randomized to either full-dose TNK-t-PA with unfractionated heparin or enoxaparin or to half-dose TNK-t-PA with abciximab and either reduced-dose unfractionated heparin or reduced-dose enoxaparin.[20] The primary endpoint of the trial was TIMI grade 3 flow at 60 min. The primary safety endpoint was TIMI major hemorrhage at 30 days. Secondary endpoints were ST-segment resolution and ischemic events.

Results indicate that enoxaparin is as effective as unfractionated heparin for achieving early reperfusion, and regimens using enoxaparin and/or abciximab are associated with higher rates of complete ST-segment resolution. The rate of major hemorrhage in the full-dose TNK arm that included unfractionated heparin was 2.4% compared with 1.9% for the arm that used full-dose TNK and enoxaparin. The major hemorrhage rate for the combination therapy arm (half-dose TNK plus abciximab) with reduced-dose unfractionated heparin was 5.2% compared with 8.5% for reduced-dose enoxaparin. No important differences were observed among the enoxaparin groups. The pooled rate of major hemorrhage for patients who received unfractionated heparin was 3.8%; for patients who received enoxaparin, the rate was 5.2%.

Phase III studies of enoxaparin need to be conducted to provide further insight into its use with combination regimens in the acute MI setting.

Integrilin and Tenecteplase in Acute Myocardial Infarction (INTEGRITI)

The INTEGRITI study assessed variable low doses of TNK and variable double-bolus doses of eptifibatide that did not include a low-molecular-weight heparin arm.[21] The primary endpoint was TIMI grade 3 flow at 60 min, and other endpoints included ST-segment resolution and TIMI myocardial perfusion grade.

Preliminary results suggest that the combination of eptifibatide and reduced-dose TNK is associated with a high degree of epicardial and myocardial reperfusion.

Discussion

Although the 30-day mortality rates achieved in GUSTO-V were statistically similar between the two treatment groups, they were the lowest rates ever observed in a large clinical trial of a fibrinolytic agent.[22] A number of factors may have contributed to the low death rate. The patient population of GUSTO-V may have been at lower risk for post-MI mortality than other populations because of patient selection for entry to the trial. Another view contends that the lower mortality rates are a reflection of better evidence-based medicine, as shown by the use of concomitant therapies such as beta blockers, angiotensin-converting enzyme inhibitors, and statins.[22]

Pertinent aspects of GUSTO-V were the findings that standard-dose abciximab plus half-dose reteplase decreased the incidence of recurrent ischemia and reinfarction as well as reduced the need for urgent revascularization compared with reteplase alone.[19] Similarly, in the ASSENT-3 trial, the abciximab arm with half-dose TNK had also significantly lower rates of in-hospital reinfarction and a reduced need for urgent PCI.[18] Although microvascular perfusion data from GUSTO-V and ASSENT-3 are not available, these results are consistent with findings from TIMI-14, which showed that abciximab plus half-dose alteplase improves epicardial and microvascular coronary blood flow in patients with acute MI.[23]

Risk of Hemorrhage

From the ASSENT-3 and GUSTO-V trials, there was no increase in ICH or stroke in patients who received the combination regimen when compared with controls.[18, 19] However, there was a significant increase in moderate or severe spontaneous non-ICH bleeding, predominantly from gastrointestinal sites. Traditional approaches to managing non-ICH bleeding and thrombocytopenia associated with combination therapy can effectively resolve these issues.

Nevertheless, the successful application of any new treatment option depends not only on its efficacy but also on its safety when compared with conventional treatment strategies. This risk could be reduced by administering lower heparin doses, or by giving greater attention to vascular access sites, with earlier removal of sheaths. Using lower doses of the thrombolytic agent and the GP IIb/IIIa receptor inhibitor, particularly in the elderly and in those with low body weight, may further reduce the bleeding risk.

Special Patient Subgroups

Based on data from the ASSENT-3 and GUSTO-V trials, the combination of a GP IIb/IIIa receptor inhibitor and low-dose lytic agent should not be administered to those aged > 75 years.[18, 19] Patients who have diabetes may also require special consideration when this potent therapeutic approach is planned and further study is warranted.

Practical Considerations

Taken together, data from the combination therapy trials provide some gauge by which decisions regarding this treatment can be made for patients with acute MI. One consideration is the timing and aggressiveness of the approach for achieving reperfusion. Current improvements in mortality and other sequelae of acute MI are based on administering therapy an average of 2.7 to 3.0 h after the onset of symptoms.[22] There

is a renewed effort to shorten the "door-to-needle time" further, given the realization that time is a critical factor in rescuing jeopardized myocardium and reducing mortality. The prehospital administration of combination therapy could, on average, save 1 h with greater potential for benefit.

Conclusion

Combination therapy is a valid option for opening occluded coronary arteries quickly and more completely. Despite initial fears that adding abciximab to thrombolytic therapy would increase ICH and stroke, this was not observed in the GUSTO-V and ASSENT-3 trials. The increased rate of non-ICH bleeding was managed appropriately. Better patient selection and care of vascular access sites may reduce this risk further. Achieving thrombolysis with combination therapy prior to PCI has the potential to restore blood flow faster and enhance outcomes in patients who lack immediate access to a catheterization laboratory, since those with TIMI grade 3 flow on arrival at the catheterization laboratory and prior to intervention appear to do better in the long term. However, until further information is available, caution should be exercised in using this potent regimen in the elderly. In addition, the use of low-molecular-weight heparin remains an interesting consideration for which further data are awaited.

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