*Note: This is a two-article spread with a shared commentary. Please scroll down for the second article.*

# Reteplase plus abciximab and reteplase alone led to similar 30-day mortality rates in acute MI

The GUSTO V Investigators. **Reperfusion therapy for acute myocardial infarction with fibrinolytic therapy or combination reduced fibrinolytic therapy and platelet glycoprotein IIb/IIIa inhibition: the GUSTO V randomised trial.** Lancet. 2001 Jun 16;357:1905-14.

## QUESTION

In patients with acute myocardial infarction (MI), what is the comparative effectiveness of half-dose reteplase plus abciximab and full-dose reteplase alone for reducing mortality?

## DESIGN

Randomized (allocation concealed*), blinded (outcome assessors),* controlled trial with 30-day follow-up for the primary outcome.

## SETTING

820 hospitals in 20 countries.

## PATIENTS

16 588 patients who were ≥ 18 years of age (mean age 61 y, 75% men) and had continuous symptoms of chest discomfort for ≥ 30 minutes and < 6 hours from onset to the time of randomization, and electrocardiographic criteria of ST-elevation MI or new left bundle-branch block. Exclusion criteria were planned catheter-based reperfusion; active bleeding or a noncompressible vascular puncture site; systolic and diastolic blood pressures > 180 mm Hg and 110 mm Hg, respectively; warfarin therapy; stroke in the previous 2 years; weight > 120 kg; or platelet count < 100 000 cells/μL. Follow-up was 98%.

## INTERVENTION

Patients were allocated to receive reteplase, two 5-U boluses given 30 minutes apart, and abciximab, a 0.25-mg/kg of body weight bolus and 0.125 μg/kg per min for 12 hours ($n$ = 8328); or reteplase, two 10-U boluses given 30 minutes apart ($n$ = 8260). All patients received aspirin and heparin.

## MAIN OUTCOME MEASURES

The main outcome was all-cause mortality at 30 days. Secondary outcomes included various complications of MI.

## MAIN RESULTS

Analysis was by intention to treat. Patients who received half-dose reteplase plus abciximab and those who received full-dose reteplase alone for all-cause mortality did not differ ($P$ = 0.43) (Table). Patients who received reteplase plus abciximab had a lower rate of the composite outcome of death or nonfatal reinfarction ($P$ = 0.001) but had a higher rate of severe or moderate nonintracranial bleeding ($P$ < 0.001) than did those who received reteplase alone (Table). The groups did not differ for the composite outcomes of cerebrovascular events or nonfatal disabling stroke, or deaths or nonfatal disabling strokes.

## CONCLUSIONS

In patients with acute myocardial infarction, half-dose reteplase plus abciximab and full-dose reteplase alone had similar 30-day mortality rates. Reteplase plus abciximab reduced the composite outcome of death or nonfatal reinfarction but increased the risk for nonintracranial bleeding.

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*See Glossary.

**Reteplase plus abciximab vs reteplase alone for acute myocardial infarction at 30 days†**

| Outcomes at 30 days | Reteplase plus abciximab | Reteplase alone | RRR (95% CI) | NNT (CI) |
|---|---|---|---|---|
| All-cause mortality | 5.6% | 5.9% | 5% (–8 to 16) | Not significant |
| Death or nonfatal reinfarction | 7.4% | 8.8% | 16% (7 to 24) | 72 (45 to 182) |
| | | | RRI (CI) | NNH (CI) |
| Nonintracranial bleeding | 4.6% | 2.3% | 98% (67 to 135) | 44 (36 to 59) |

†Abbreviations defined in Glossary; RRR, RRI, NNT, NNH, and CI calculated from data in article.

## COMMENTARY

The 2 latest large thrombolytic trials, GUSTO V and ASSENT-3, have used combination antithrombotic regimens to further reduce death caused by MI by more rapidly and fully restoring coronary patency.

2 previous pilot studies (1, 2) suggested that a half-dose thrombolytic plus platelet inhibition with full-dose abciximab, in addition to aspirin and reduced-dose heparin, was associated with greater early patency than the prototype full-dose thrombolytic. The GUSTO V and ASSENT-3 studies tested this combination therapy to verify that enhanced early patency improved survival and reduced reinfarction without increasing bleeding.

Surprisingly, GUSTO V failed to show reduced mortality with combination therapy. However, it showed a reduced incidence of reinfarction, which provides some support for the concept. The combination was associated with a modest, but significant, increase in bleeding but fortunately not with an increase in brain hemorrhage.

ASSENT-3 was a smaller and less ambitious trial than GUSTO V and used a composite primary end point. ASSENT-3 showed more positive results than did GUSTO V; reduced-dose TNK plus abciximab was more beneficial than TNK alone, with a slight increase in bleeding (not cerebral bleeding). However, the effects on mortality alone were not evaluated. The biggest surprise was that the enoxaparin-plus-TNK combination showed the best results.

Several questions remain. Although it seems that TNK is better than reteplase for combined therapy with abciximab, this has not been proved in a head-to-head comparison study. Ongoing trials are testing other platelet inhibitors (e.g., eptifibatide and tirofiban) with half-dose TNK to see whether these small molecules show better results than does abciximab (3). The paradox is that with more data

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# Tenecteplase plus enoxaparin or abciximab was better than tenecteplase plus unfractionated heparin for acute MI

The Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-3 Investigators. **Efficacy and safety of tenecteplase in combination with enoxaparin, abciximab, or unfractionated heparin: the ASSENT-3 randomised trial in acute myocardial infarction.** Lancet. 2001 Aug 25;358:605-13.

### QUESTION

In patients with acute myocardial infarction (MI), what is the efficacy and safety of tenecteplase (TNK) plus enoxaparin, TNK plus unfractionated heparin (UFH), or half-dose TNK plus abciximab?

### DESIGN

Randomized (allocation concealed*), blinded (assessors of stroke outcomes),* controlled trial with 30-day follow-up.

### SETTING

575 hospitals in 26 countries.

### PATIENTS

6095 patients who were ≥ 18 years of age (mean age 61 y, 76% men) and had acute MI of < 6 hours, ST-segment elevation ≥ 0.1 mV in ≥ 2 limb leads or ≥ 0.2 mV in ≥ 2 contiguous precordial leads, or left bundle-branch block. Exclusion criteria included elevated blood pressure, recent glycoprotein IIb or IIIa inhibitor use, and various other diseases and conditions. Follow-up was 99.9%.

### INTERVENTION

Patients were allocated to receive full-dose TNK plus enoxaparin (enoxaparin was given intravenously as a 30-mg bolus and subcutaneously at 1 mg/kg of body weight every 12 h for up to 7 d) (enoxaparin group, $n$ = 2040); half-dose TNK plus weight-adjusted low-dose UFH plus abciximab (abciximab was given as a 0.25 mg/kg bolus and 0.125 μg/kg per min infusion for 12 h) (abciximab group, $n$ = 2017); or full-dose TNK plus UFH (UFH was given as a 60 U/kg bolus and 12 U/kg per h infusion for 48 h) (UFH group, $n$ = 2038). Full TNK doses ranged between 30 and 50 mg, and half doses ranged between 15 and 25 mg, according to body weight.

### MAIN OUTCOME MEASURES

Main outcomes were the composite end point of 30-day mortality, in-hospital re-infarction, or in-hospital refractory ischemia (composite efficacy end point) and the composite end point that included the composite efficacy end point plus in-hospital intracranial hemorrhage or in-hospital major bleeding (composite efficacy plus safety end point).

### MAIN RESULTS

Analysis was by intention to treat. Lower rates of the composite efficacy end point were seen in the enoxaparin ($P$ < 0.001) and abciximab groups ($P$ < 0.001) than in the UFH group. Similarly, lower rates of the composite efficacy plus safety end point were seen in the enoxaparin ($P$ = 0.003) and abciximab groups ($P$ = 0.014) than in the UFH group.

### CONCLUSION

In patients with acute myocardial infarction, tenecteplase plus enoxaparin and half-dose tenecteplase plus abciximab and unfractionated heparin were more effective and safe than tenecteplase plus unfractionated heparin.

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*See Glossary.

**Tenecteplase plus enoxaparin or abciximab vs unfractionated heparin (UFH) for acute myocardial infarction at 30 days†**

| Outcomes | Comparisons | Event rates | RRR (95% CI) | NNT (CI) |
|---|---|---|---|---|
| Composite efficacy end point | Enoxaparin vs UFH | 11% vs 15% | 26% (13 to 37) | 25 (16 to 53) |
| | Abciximab vs UFH | 11% vs 15% | 28% (16 to 39) | 23 (16 to 44) |
| Composite efficacy plus safety end point | Enoxaparin vs UFH | 14% vs 17% | 19% (7 to 30) | 30 (18 to 92) |
| | Abciximab vs UFH | 14% vs 17% | 16% (4 to 28) | 36 (20 to 175) |

†Composite efficacy end point = mortality, in-hospital reinfarction, or in-hospital refractory ischemia; composite efficacy plus safety end point = composite efficacy end point plus in-hospital intracranial hemorrhage or in-hospital major bleeding. Other abbreviations defined in Glossary; RRR, NNT, and CI calculated from data in article.

## COMMENTARY *(continued from page 42)*

clinicians face greater decision-making challenges and need to consider greater ranges of available choices, diminishing returns, high cost, and formulary restrictions.

How should patients with ST-elevation MI be treated if primary angioplasty is not immediately available? Aspirin, TNK, and enoxaparin seem to offer the best combination of favorable results, safety, and simplicity. However, combination half-dose lytic and abciximab therapy may be advantageous in patients who are < 75 years of age because of reduced reinfarction and less bleeding than in the elderly.

Eptifibatide and tirofiban should not be substituted for abciximab until more comparison studies become available. Most important, clinicians making changes in their thrombolytic formulations should not neglect the basic treatment methods of aspirin, β-blockers, angiotensin-converting enzyme inhibitors, statins, and smoking cessation.

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***References***

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3. **Simoons ML.** Effect of glycoprotein IIb/IIIa receptor blocker abciximab on outcome in patients with acute coronary syndromes without early coronary revascularisation: the GUSTO IV-ACS randomised trial. Lancet 2001;357:1915-24.

  