Prognostic implication of activated partial thromboplastin time after reteplase or half-dose reteplase plus abciximab: results from the GUSTO-V trial


Aims To evaluate the relationship between activated partial thromboplastin time (aPTT) and clinical outcomes in the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO-V) trial comparing standard-dose reteplase to half-dose reteplase and abciximab.

Methods and results We analysed data on 11,420 patients receiving unfractionated heparin. Peak aPTT levels recorded during the hospitalization were correlated with clinical outcomes. Multivariable logistic regression models examined the relationship between peak aPTT levels and (i) moderate-to-severe bleeding, (ii) intracerebral haemorrhage, (iii) reinfarction, and (iv) 30-day mortality. Non-linear relationships were explored in the models using cubic spline functions. Higher rates of significant complications were seen in both groups when aPTT levels were >50 s or when levels were >70 s. In the combination therapy group, the relationship between aPTT levels and bleeding appeared accentuated. Reinfarction rates increased gradually as aPTT levels were >70 s in both groups, but the relationships were not statistically significant. Peak aPTT levels >50 s were associated with increased 30-day mortality even after multivariable adjustment.

Conclusion Peak aPTT levels >50 s and >70 s are associated with worse clinical outcomes in the modern era of fibrinolytic therapy; these relationships are different in patients receiving standard reteplase vs. combination therapy.

Introduction

The ideal dosing regimen for unfractionated heparin (UFH) after fibrinolytic therapy for acute ST-segment elevation myocardial infarction (STEMI) remains uncertain despite its widespread use. Granger et al. noted a strong relationship between 12 h activated partial thromboplastin times (aPTTs) over 70 s and bleeding complications among nearly 30,000 patients receiving UFH in the Global Utilization of Streptokinase and tissue plasminogen activator (t-PA) for Occluded Coronary Arteries (GUSTO-I) trial. It was also observed that prolonged aPTTs were paradoxically associated with an increased risk of reinfarction. Both findings appeared to translate into an overall increased risk of death at 30 days for patients with aPTTs over 70 s. These results led, in part, to current recommendations that UFH dosing after fibrinolytic therapy be targeted for aPTTs between 50 and 70 s.

Recently, a combination pharmacological approach to reperfusion for STEMI using half-dose fibrinolytic therapy, glycoprotein IIb/IIIa receptor antagonists, and UFH has been investigated. The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO)-V trial evaluated clinical outcomes in 16,588 patients randomly assigned to standard-dose reteplase or half-dose reteplase plus abciximab. Both
groups received intravenous UFH. The purpose of this analysis was to investigate the impact of aPTT levels on clinical outcomes among patients in GUSTO-V. In particular, we were interested in determining whether important differences in outcomes existed between the standard-dose reteplase and combination therapy groups.

Methods

Study population and protocol

Details of the GUSTO-V trial have been previously reported. Briefly, 16 588 patients >18 years old were enrolled at 820 hospitals in 20 countries between July 1999 and February 2001. Inclusion criteria were chest discomfort for at least 30 min, but <6 h before randomization, and associated electrocardiographic ST-segment elevation or new left bundle branch block. Patients for whom immediate catheter-based reperfusion was planned were excluded. Other exclusion criteria included active bleeding or haemorrhagic diathesis, thrombocytopenia, ongoing warfarin therapy, use of a glycoprotein IIb/IIIa receptor antagonist during the previous 7 days, systolic blood pressure <110 mmHg or diastolic blood pressure >110 mmHg, history of recent non-haemorrhagic stroke or any haemorrhagic stroke, structural central nervous system abnormality, recent major surgery or trauma, and non-compressible vessel puncture within 24 h. Institutional review board approval was obtained from each clinical site and all patients provided written informed consent.

Patients were randomly assigned to (i) standard-dose reteplase (two 10 U intravenous boluses, 30 min apart) or (ii) combination therapy using half-dose reteplase (two 5 U boluses, 30 min apart) with abciximab [0.25 mg/kg bolus followed by a 0.125 μg/kg per minute infusion (maximum 10 μg/min) for 12 h]. Additionally, all patients were treated with aspirin. For patients receiving standard-dose reteplase, UFH was given in a 5000 U bolus followed by a 1000 U/h (or 800 U/h for patients with body weights <80 kg) infusion. A 60 U/kg bolus of UFH (maximum dose, 5000 U) followed by a 7 U/kg per hour infusion was given in the combination therapy group. The lower dose of UFH in the combination therapy group was used to compensate for the anticoagulant effect of abciximab. UFH doses were adjusted according to a standard nomogram to maintain aPTTs between 50 and 70 s (Table 1). The study protocol recommended the use of UFH for a minimum of 24 h but allowed for physician discretion. Routine aPTT measurement was performed every 6 h during UFH infusion. All other medications and therapies (i.e. use of coronary angiography or intervention) were left to the judgment of the treating physicians.

aPTT assessment and study endpoints

For these analyses, we excluded patients who: (i) received low-molecular weight heparin at any point during their hospitalization (n = 4627), (ii) did not receive UFH (n = 66), or (iii) had no peak aPTT level measured (n = 475). The primary endpoint of GUSTO-V was overall 30-day mortality. Additional endpoints assessed at 7 days or discharge (whichever occurred first) included moderate-to-severe bleeding, intracerebral haemorrhage, and reinfarction. Bleeding was considered moderate if it required transfusion but was not associated with haemodynamic compromise. Severe bleeding was associated with haemodynamic compromise. Possible stroke, including intracerebral haemorrhage, was adjudicated by a neurologist who was blinded to treatment allocation. Reinfarction required new significant electrocardiographic changes, elevations in cardiac biomarkers, or both.

Statistical analyses

Baseline characteristics were reported as medians with interquartile ranges for continuous variables and frequencies for categorical variables. Univariate comparisons between groups of patients stratified by treatment assignment and peak aPTT levels (<50, 50–70, >70 s) were performed using non-parametric Kruskal–Wallis equality tests and χ² tests.

We used logistic regression to model the association between peak aPTT levels and moderate-to-severe bleeding, intracerebral haemorrhage, reinfarction, and 30-day mortality. Non-linear relationships were explored using cubic spline functions, and then appropriate linear spline functions were used in the models. For moderate-to-severe bleeding, intracerebral haemorrhage, and reinfarction, the analyses were adjusted for age, gender, and weight. In the analysis of 30-day mortality, we adjusted for age and gender, and also included other covariates such as previous myocardial infarction, the use of nitrates in <48 h, blood pressure, pulse, Killip classification, infarct location, and time to reperfusion therapy in the final model. Interaction terms were included in the models to determine whether the associations varied between treatment groups. All statistical tests were two-sided, and a P-value of <0.05 was used to determine statistical significance.

Results

Clinical characteristics

Clinical characteristics of the 11 420 patients included in the analysis are listed in Table 2. The combination therapy group had a higher percentage of patients with hypertension and hyperlipidaemia, but other characteristics including age, gender, median body mass index (BMI), and weight were similar across both groups. Peak aPTT values were higher (median, 87.3 vs. 66.0 s; P < 0.001) and more rapidly reached (median, 7.2 vs. 19.3 h; P < 0.001) in patients receiving standard-dose reteplase compared with combination therapy.

Table 3 lists clinical characteristics in the standard-dose reteplase and combination therapy groups stratified by peak aPTT level. Patients receiving standard-dose reteplase were more likely to have peak aPTT levels >70 s (3794/5645 or 66.2 vs. 2592/5775 or 44.9%; P < 0.001). In both groups, patients with peak aPTT levels >70 s were more often older and women, had lower body weights and BMIs, and were less likely to smoke cigarettes when compared to those with lower peak aPTT levels. Peak aPTT levels over 70 s in the standard-dose reteplase group were also associated with a higher incidence of hypertension than aPTT levels between 50 and 70 s, whereas peak aPTT levels >70 s in the combination therapy group were associated with more hypertension and hyperlipidaemia.
Moderate-to-severe bleeding and intracerebral haemorrhage

Rates of moderate-to-severe bleeding increased with higher peak aPTT levels in both the standard-dose reteplase and the combination therapy groups (Figure 1A and B). The risk appeared to rise only gradually in the standard-dose reteplase group as peak aPTT levels increased (peak aPTT levels >70 s, \( P < 0.001 \)) but more dramatically in the combination therapy group (peak aPTT levels >70 s, \( P = 0.004 \)). This group of patients also appeared to have a higher risk of bleeding at lower peak aPTT levels (peak aPTT levels <50 s, \( P < 0.001 \)), likely because of early bleeding complications that required the rapid discontinuation of UFH. Absolute rates of bleeding were consistently higher in the combination therapy group across all aPTT levels.

Peak aPTT levels appeared to have a less consistent relationship with the development of intracerebral haemorrhage (Figures 2A and B) at higher levels in both the standard-dose reteplase group (peak aPTT levels >70 s, \( P = 0.250 \)) and the combination therapy group (peak aPTT levels >70 s, \( P = 0.672 \)). Lower peak aPTT levels were associated with higher intracerebral haemorrhage rates in the combination therapy group (peak aPTT levels <50 s, \( P < 0.001 \)).

Reinfarction and 30-day mortality

Reinfarction rates were higher in patients receiving standard-dose reteplase when compared with those in the combination therapy group. Although reinfarction rates appeared to increase gradually as peak aPTT levels were >70 s in the standard-dose reteplase group (Figure 3A) compared with the combination therapy group (Figure 3B), neither relationship was statistically significant (standard-dose reteplase group, \( P = 0.757 \); combination therapy group, \( P = 0.369 \)). Figure 4A and B shows the association between 30-day mortality and peak aPTT levels. In the standard-dose reteplase group, unadjusted 30-day mortality rates decreased as peak aPTT levels approached 50 s (\( P < 0.001 \)) and only gradually rose at higher levels (peak aPTT levels >70 s, \( P = 0.472 \)). A similar relationship was seen at lower peak aPTT levels in the combination therapy group (peak aPTT levels <50 s, \( P < 0.001 \)) but with a more dramatic rise in 30-day mortality rates at higher peak aPTT levels (peak aPTT levels >70 s, \( P = 0.008 \)).

After adjustment for demographics, cardiovascular risk factors, presenting characteristics, and treatment assignment, the relationship between peak aPTT levels and 30-day mortality demonstrated a significant decrease in mortality risk as levels approached 50 s (odds ratio, 0.94

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**Table 2** Clinical characteristics by treatment group

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Standard-dose reteplase</th>
<th>Reteplase + abciximab</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 5645)</td>
<td>(n = 5775)</td>
<td></td>
</tr>
<tr>
<td>Age &gt;70 years, n (%)</td>
<td>1359 (24.1)</td>
<td>1473 (25.5)</td>
<td>0.08</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>1363 (24.2)</td>
<td>1433 (24.8)</td>
<td>0.41</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>1833 (32.7)</td>
<td>2020 (35.3)</td>
<td>0.003</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>849 (15.2)</td>
<td>904 (15.8)</td>
<td>0.36</td>
</tr>
<tr>
<td>Hyperlipidaemia, n (%)</td>
<td>924 (16.9)</td>
<td>1027 (18.4)</td>
<td>0.03</td>
</tr>
<tr>
<td>Smoker, n (%)</td>
<td>2645 (47.3)</td>
<td>2634 (46.1)</td>
<td>0.21</td>
</tr>
<tr>
<td>Prior MI, n (%)</td>
<td>824 (14.8)</td>
<td>866 (15.2)</td>
<td>0.48</td>
</tr>
<tr>
<td>Prior CHF, n (%)</td>
<td>147 (2.7)</td>
<td>137 (2.5)</td>
<td>0.44</td>
</tr>
<tr>
<td>Prior bypass surgery, n (%)</td>
<td>201 (3.6)</td>
<td>192 (3.4)</td>
<td>0.50</td>
</tr>
<tr>
<td>Prior PCI, n (%)</td>
<td>393 (7.0)</td>
<td>371 (6.5)</td>
<td>0.27</td>
</tr>
<tr>
<td>BMI (median)</td>
<td>26.6</td>
<td>26.6</td>
<td>0.31</td>
</tr>
<tr>
<td>Weight [kg (median)]</td>
<td>79.0</td>
<td>78.0</td>
<td>0.18</td>
</tr>
<tr>
<td>Peak aPTT (s)</td>
<td>87.3</td>
<td>66.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time to peak aPTT (h)</td>
<td>7.2</td>
<td>19.3</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CHF, congestive heart failure; MI, myocardial infarction.

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**Table 3** Clinical characteristics of reteplase only and combination therapy groups by peak aPTT

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Standard-dose reteplase</th>
<th>Combination therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(&lt;50 \text{s} (n = 523))</td>
<td>(\geq 50 \text{s} (n = 1274))</td>
</tr>
<tr>
<td>Age &gt;70 years, n (%)</td>
<td>75 (14.3)</td>
<td>284 (22.3)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>86 (16.4)</td>
<td>256 (20.1)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>179 (34.5)</td>
<td>430 (34.1)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>95 (18.6)</td>
<td>195 (15.5)</td>
</tr>
<tr>
<td>Hyperlipidaemia, n (%)</td>
<td>73 (15.5)</td>
<td>198 (16.1)</td>
</tr>
<tr>
<td>Smoker, n (%)</td>
<td>283 (54.8)</td>
<td>636 (50.4)</td>
</tr>
<tr>
<td>BMI (median)</td>
<td>27.8</td>
<td>26.8</td>
</tr>
<tr>
<td>Weight [kg (median)]</td>
<td>84.0</td>
<td>80.0</td>
</tr>
</tbody>
</table>

\(^a\)P-value comparing clinical characteristics within treatment groups.

\(^b\)P-value comparing clinical characteristics between treatment groups.
for each 1 s increase in peak aPTT <50 s when compared with a peak aPTT level of 50 s; 95% confidence interval, 0.92–0.95; \( P < 0.001 \). There was no association after multivariable adjustment between peak aPTT levels and mortality risk at 30 days, when peak aPTT levels rose from 50 to 70 s \( (P = 0.461) \) or when levels were >70 s \( (P = 0.260) \). These findings were consistent for patients, regardless of treatment assignment.

**Discussion**

**Main findings**

Our study has three main findings. First, we noted that older age, female gender, lower body weight, and lack of cigarette smoking were associated with higher peak aPTT levels in patients with STEMI receiving UFH. These relationships were consistent regardless of whether the patients received standard-dose reteplase or combination therapy with half-dose reteplase and abciximab, and importantly, agree with results from GUSTO-I. In addition, higher peak aPTT levels were common overall, whereas they occurred less frequently in the combination therapy group despite the use of abciximab in those patients. The time to peak aPTT level was also longer in the combination group. These findings likely reflect the use of lower weight-based UFH dosing in the combination therapy group as opposed to a standard UFH dosing regimen. If over-anticoagulation occurred in the standard-dose reteplase group because of higher UFH doses, differences in outcomes like bleeding between the two groups may have been less than anticipated.

Secondly, we noted relationships between peak aPTT levels and rates of bleeding complications, reinfarction, and 30-day mortality in patients treated with standard-dose reteplase and UFH. The relationship between peak aPTT levels and most clinical outcomes was remarkably similar to that of 12 h aPTT levels in GUSTO-I, where streptokinase and t-PA were the fibrinolytic agents. An important exception was that no relationship between peak aPTT levels and 30-day mortality was detected after multivariable adjustment.

Thirdly, we found the association between peak aPTT levels and outcomes to be somewhat different in patients receiving combination therapy. In the combination therapy group, rates of moderate-to-severe bleeding appeared to rise more dramatically as peak aPTT levels were >70 s when compared with patients receiving standard-dose reteplase. In contrast, reinfarction rates were lower in the combination therapy group regardless of aPTT level, which may be related to enhanced antiplatelet
activity with glycoprotein IIb/IIIa receptor antagonists or significant reductions in prothrombin activation and thrombin generation when compared with standard-dose reteplase. Whether these effects are due to a decrease in reteplase dose or the addition of abciximab, however, remains unknown.

The pattern of increased bleeding rates and lower reinfarction rates in the combination therapy group is similar to the initial clinical experience with abciximab during percutaneous coronary intervention. In the Evaluation in PTCA to Improve Long-Term Outcome with Abciximab GP IIb/IIIa Blockade (EPILOG) study, however, low-dose UFH with abciximab was ultimately shown to maintain reductions in ischaemic outcomes while minimizing major bleeding events compared with standard-dose UFH with abciximab. Presently, when glycoprotein IIb/IIIa inhibitors are administered during elective percutaneous coronary intervention, low-dose UFH is routinely used with decreased activated clotting time and aPTT targets. Although purely speculative, outcomes in the combination therapy group in GUSTO-V may have been improved had even lower doses of UFH been administered.

It remains unclear as to why bleeding rates would be higher in patients with lower aPTT levels in the combination therapy group. This is most likely due to the observational nature of our data. Patients that develop early bleeding complications are very likely to have their UFH discontinued rapidly resulting in low peak aPTT levels. In contrast to the GUSTO-I study, we did not find statistical evidence for higher reinfarction rates with elevated aPTT levels.

The relationship between aPTT levels and clinical outcomes in non-ST segment elevation acute coronary syndromes has also been investigated. In the GUSTO-IIb study, 12 h aPTT levels were associated with higher rates of moderate-to-severe bleeding and a composite endpoint of 30-day death or reinfarction. Anand et al. recently reported similar results in the Organization to Assess Strategies for Ischaemic Syndromes (OASIS)-2 study. In that analysis, higher mean aPTT levels over a 72 h period were associated with increased bleeding events but levels <60 s were associated with an increased risk of recurrent cardiovascular events and refractory angina. Importantly, this latter relationship between mean aPTT levels and recurrent cardiovascular events was not present when the
authors performed the analysis using levels as a continuous variable as in our study.

Limitations

Our study must be interpreted in the context of the following limitations. First, we were able to correlate clinical outcomes only with peak aPTT levels. The lack of data on aPTT levels at specific time intervals left us unable to comment on the overall adequacy of anticoagulation following fibrinolytic therapy. In addition, peak aPTT levels are susceptible to other factors such as inflammation and the timing of sampling. As suggested previously, patients with elevated peak aPTT levels may have had UFH doses lowered rapidly or even discontinued abruptly leading to insufficient anticoagulant effects. The fact that our results in the standard-dose reteplase group matched those from GUSTO-I (which used 12 and 24 h aPTT levels), however, suggest that our findings may not have been substantially biased.\(^2\) The exclusion of patients without peak aPTT measurements also might have biased our results. This group of patients had a higher mortality rate at 6 h than in patients with peak aPTT measurements (24.1 vs. 0.5%), which may explain why levels were unavailable.

Secondly, our data set did not include information on the overall dose of UFH used or the exact time of its discontinuation. The study protocol for GUSTO-V called for UFH to be used for 24 h in most cases but provided treating physicians with discretion for longer periods of use. Studies associating UFH duration with outcomes have not shown consistent findings. In the Platelet Ib/IIIa in Unstable Angina: Receptor Suppression Using Integrin Therapy (PURSUIT) trial,\(^14\) it appeared that longer periods of UFH duration were positively correlated with rebound events only when UFH was discontinued in patients not actively receiving eptifibatide, a glycoprotein Ib/IIIa receptor inhibitor.

Thirdly, the lack of standardization of aPTT measurement across centres is important to note. As others have argued,\(^2,12\) however, the value of correlating aPTT levels to clinical outcomes across such a broad range of institutions confers generalizability to our results, which may outweigh limitation relating to standardization. Finally, our analysis was primarily descriptive in nature. Although we were able to show associations between peak aPTT levels and outcomes such as bleeding and 30-day mortality, it is not possible for us to comment on how (and if) treatment with UFH should be altered when aPTT levels return elevated. Our data do suggest, however, that when UFH is used after fibrinolytic therapy, care be used to ensure that aPTT levels do not exceed 70 s. This appears to be even more critical when concomitant therapy with glycoprotein Ib/IIIa inhibitor is considered. It is also of note that patients in the combination therapy group were less frequently over-anticoagulated despite the use of abciximab, potentially because of the use of lower weight-based UFH dosing.

Finally, there has been increasing interest in the use of low-molecular weight heparin for anticoagulation following fibrinolytic therapy.\(^5,15\) Given its relatively specific effects, low-molecular weight heparin does not have a substantial impact on aPTT levels but instead lowers anti-Xa levels. There is also provocative evidence in patients with non-ST segment elevation acute coronary syndromes that low anti-Xa levels may be associated with worse clinical outcomes but high anti-Xa levels are not related to major bleeding.\(^16\) We eliminated all cases in which low-molecular weight heparin was used from our analysis. Until use of these agents becomes better established, however, our results will have clinical relevance for most patients receiving fibrinolytic therapy for STEMI.

Conclusion

Our study suggests that both high and low aPTT levels continue to be associated with adverse clinical outcomes in the modern era of fibrinolytic therapy. Although we found that outcomes were associated with peak aPTT levels in both treatment groups in GUSTO-V, aPTT thresholds appeared to be different between patients receiving standard-dose reteplase and combination therapy.

Supplementary material

Supplementary material is available at European Heart Journal online.

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References


