Relationship Between Activated Clotting Time and Ischemic or Hemorrhagic Complications

Analysis of 4 Recent Randomized Clinical Trials of Percutaneous Coronary Intervention

Sorin J. Brener, MD; David J. Moliterno, MD; A. Michael Lincoff, MD; Steven R. Steinhubl, MD; Kathy E. Wolski, MS; Eric J. Topol, MD

Background—Unfractionated heparin (UFH) is the most widely used antithrombin during percutaneous coronary intervention (PCI). Despite significant pharmacological and mechanical advancements in PCI, uncertainty remains about the optimal activated clotting time (ACT) for prevention of ischemic or hemorrhagic complications.

Methods and Results—We analyzed the outcome of all UFH-treated patients enrolled in 4 large, contemporary PCI trials with independent adjudication of ischemic and bleeding events. Of 9974 eligible patients, maximum ACT was available in 8369 (84%). The median ACT was 297 seconds (interquartile range 256 to 348 seconds). The incidence of death, myocardial infarction, or revascularization at 48 hours, by ACT quartile, was 6.2%, 6.8%, 6.0%, and 5.7%, respectively (P=0.40 for trend). Covariate-adjusted rate of ischemic complications was not correlated with maximal procedural ACT (continuous value, P=0.29). Higher doses of UFH (>5000 U, or up to 90 U/kg) were independently associated with higher rates of events. The incidence of major or minor bleeding at 48 hours, by ACT quartile, was 2.9%, 3.5%, 3.8%, and 4.0%, respectively (P=0.04 for trend). In a multivariable logistic model with a spline transformation for ACT, there was a linear increase in risk of bleeding as the ACT approached 365 seconds (P=0.01), which leveled off beyond that value. Increasing UFH weight-indexed dose was independently associated with higher bleeding rates (OR 1.04 [1.02 to 1.07] for each 10 U/kg, P=0.001).

Conclusions—In patients undergoing PCI with frequent stent and potent platelet inhibition use, ACT does not correlate with ischemic complications and has a modest association with bleeding complications, driven mainly by minor bleeding. Lower values do not appear to compromise efficacy while increasing safety.

Key Words: angioplasty ♦ heparin ♦ ischemia ♦ hemorrhage

Despite the development of new intravenous anticoagulants that affect the thrombin cascade, unfractionated heparin (UFH) remains the most commonly used agent during percutaneous coronary intervention (PCI). Significant debate remains, however, with regard to the correlation between the effects of UFH, measured as the activated clotted time (ACT), and ensuing ischemic and hemorrhagic complications. Some older series and historical consensus have reported that higher ACTs (at least 300 seconds) are needed to combat immediate ischemic complications, such as abrupt vessel closure, even at the cost of a higher bleeding rate.1–5 In contrast, newer analyses from a PCI environment in which stents are nearly universally used, intravenous glycoprotein (GP) IIb/IIIa inhibitors are frequently used to provide instantaneous potent platelet inhibition, and thienopyridines are increasingly prescribed before PCI have challenged these assumptions.6,7 A recent report from a single institution claimed that only minute doses of UFH are needed during uncomplicated stent implantation.8 Additional complexity is added by the relative weak correlation between the UFH dose administered and the ACT and by the variability in instruments used to measure ACT.

Thus, we combined 4 large randomized, clinical trials of PCI (Clopidogrel for the Reduction of Events During Observation [CREDO],9 Tirofiban And Reopro Give similar Efficacy outcomes Trial [TARGET],10 and Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events [REPLACE] 11a and 21b) performed between June 1999 and August 2002 at hundreds of medical centers on 4 continents. We analyzed the relationship between peak ACT measured during PCI and the incidence of (1) ischemic events at 48 hours (death, myocardial infarction [MI], or target-vessel revascularization [TVR]) and (2) bleeding complications with the Thrombolysis In Myocardial Infarction (TIMI) classification.10

Methods

The 4 trials have been described in detail. In brief, in TARGET, 4809 patients undergoing elective or urgent PCI with stent implantation...
were randomly assigned to tirofiban or abciximab in a double-blind fashion. Aspirin and clopidogrel were administered before the procedure. UFH in a dose of 70 U/kg was intended to achieve an ACT of 250 seconds (5 minutes after bolus). In CREDO, 2116 patients likely to undergo elective or urgent PCI were randomly assigned (double blind) to UFH (65 U/Kg with either abciximab or eptifibatide) or bivalirudin. Only the UFH arm was included in this analysis. Clopidogrel and GP IIb/IIIa antagonists were given at the discretion of the investigator. In REPLACE-1, 1056 patients undergoing elective or urgent PCI were randomly assigned (open label) UFH (60 to 70 U/kg, target ACT 200 to 300 seconds) or bivalirudin. Only the UFH arm was included in this analysis. Clopidogrel and GP IIb/IIIa antagonists were given at the discretion of the investigator. In REPLACE-2, 6010 patients undergoing elective or urgent PCI were randomly assigned (double blind) to UFH (65 U/Kg with either abciximab or eptifibatide) or bivalirudin. Only the UFH arm was included in this analysis. An ACT (5 minutes after bolus) of at least 225 seconds was targeted. All patients received aspirin and clopidogrel for 1 month after PCI. UFH and GP IIb/IIIa antagonists were given at the discretion of the investigator. In REPLACE-1, 1056 patients undergoing elective or urgent PCI were randomly assigned (open label) UFH (60 to 70 U/kg, target ACT 200 to 300 seconds) or bivalirudin. Only the UFH arm was included in this analysis. Clopidogrel and GP IIb/IIIa antagonists were given at the discretion of the investigator. In REPLACE-2, 6010 patients undergoing elective or urgent PCI were randomly assigned (double blind) to UFH (65 U/Kg with either abciximab or eptifibatide) or bivalirudin. Only the UFH arm was included in this analysis. An ACT (5 minutes after bolus) of at least 225 seconds was targeted. All patients received aspirin, and pretreatment with clopidogrel was strongly encouraged. We excluded patients who did not undergo PCI (n=483). In all trials, the primary efficacy end point included a composite of death, MI, or TVR. MI after PCI was defined as either new Q waves or an increase in creatine kinase-MB >3 times the upper limit of normal. Bleeding was monitored using the TIMI minor and major bleeding definitions. To account for the influence of red blood cell transfusions on hemoglobin values, estimated decreases in hemoglobin were adjusted according to the technique described by Landefeld et al.2 We censored both types of events at 48 hours. The same independent Clinical Events Committee reviewed all clinical events.

ACTs were measured using primarily the Hemochron Jr device (ITC; REPLACE 1 and 2, TARGET; device not specified in CREDO), as shown in the Table.

### Statistical Methods
Continuous and discrete variables were analyzed with standard parametric tests. Mantel-Haenszel χ2 test for trend was used to univariately examine the relationship between ACT quartile and the ischemic and bleeding end points. Multivariable logistic regression analysis for safety and efficacy end points was performed considering variables available in all trials: age; gender; race; smoking (current or within 1 year); hypertension; diabetes mellitus; history of MI, PCI, CABG, congestive heart failure, or cerebrovascular disease; indication for PCI (unstable versus stable angina); concomitant use of GP IIb/IIIa antagonists; and pretreatment with clopidogrel. ACT value was treated as a continuous variable. Doses of UFH were recorded as total and were weight-indexed in each trial and treated as continuous variables. Spline transformations were applied when relationships between continuous variables and outcome changed at certain thresholds.

### Results
There were 9974 patients in the 4 trials that qualified for this analysis. ACT data were available in 8369 (84%). An ACT was recorded in all REPLACE-1 patients and was missing in 2.5% in REPLACE-2, 25% in TARGET, and 20% in CREDO. Patients without measured ACT had a significantly lower incidence of MI than those with ACT (4.3% versus 5.8%, P=0.02). Their incidence of major or minor bleeding was 3.1% versus 3.5% in those with ACT (P=0.41). The key baseline and procedural characteristics are shown in the Table. The average ACT was 315±148 seconds (median 297 seconds, interquartile range 256 to 348 seconds). ACT <220 seconds was noted in 9.1%, and 20.6% had ACT >360 seconds. The incidence of death or MI or the composite of death, MI, or TVR did not vary significantly among ACT quartiles (P=0.40 and P=0.33 for trend, respectively; Figure 1). A multivariable logistic regression model that included patients with documented ACT confirmed the lack of significant correlation between maximum ACT and ischemic events at 48 hours (P=0.29; Figure 2). There was no statistical interaction with diabetes mellitus, unstable angina, or any other variable included in the model. Substituting the ACT for the total dose of heparin revealed a complex relationship. Up to a total of 5000 U, there was no association with ischemic events, whereas higher doses were associated with more events (OR 1.005 per 100 U, P<0.001). Higher weight had a marginally protective effect (OR 0.995 per kg, P=0.052). In the same vein, increasing doses of UFH up to 90 U/kg were associated with more events (OR 1.14 per 10 U/kg, P<0.001), whereas higher doses (>90 U/kg) were no longer statistically associated with more events (P=0.99). Considering that the average total dose of UFH in the

### Table: Key Baseline and Procedural Characteristics of 4 PCI Trials

<table>
<thead>
<tr>
<th></th>
<th>REPLACE-1 Heparin</th>
<th>REPLACE-2 Heparin</th>
<th>TARGET Abciximab</th>
<th>TARGET Tirofiban</th>
<th>CREDO Placebo</th>
<th>CREDO Clopidogrel</th>
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<td>No. of patients</td>
<td>9974</td>
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<td>2896</td>
<td>2374</td>
<td>2371</td>
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<td>63±11</td>
<td>63±11</td>
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<td>26</td>
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<td>26</td>
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<td>Hypertension, %</td>
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<td>23</td>
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<td>21</td>
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<td>31</td>
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<td>Prior MI, %</td>
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<td>40</td>
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<td>Prior PCI, %</td>
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<td>30</td>
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<td>19</td>
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<td>100</td>
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<td>Prior clopidogrel use, %</td>
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<td>93</td>
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<td>6.2±2.3</td>
<td>5.8±1.1</td>
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<td>6.3±2.7</td>
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<td>Total UFH, U/kg</td>
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<td>Hemochron use, % (n=8115)</td>
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</table>
trials was >6000 U, the 2 models described above are congruent. Regardless of whether ACT or heparin dose was entered in the multivariable models, the same variables had an independent effect on the incidence of ischemic events; increasing age, prior MI, unstable angina, and GP IIb/IIIa use (likely a marker of higher-risk patients) were associated with higher rates of events, whereas prior PCI and pretreatment with clopidogrel were protective ($P<0.05$ for both). There was no correlation between maximum ACT and weight-adjusted UFH dose ($R^2<0.1$).

TIMI major bleeding was infrequent and not statistically different among the ACT quartiles ($P=0.22$ for trend; Figure 3). The addition of minor bleeding to the safety end point resulted in a significant but complex association with ACT ($P=0.04$ for trend; Figure 3). Multivariable logistic regression using spline transformation of ACT revealed that up to an ACT of 365 seconds, there was a significant association between higher ACT and major or minor bleeding ($P=0.01$; Figure 4). Beyond that level, the correlation of bleeding events with ACT became insignificant ($P=0.09$), demonstrating an inverse relationship between higher ACT and bleeding.

Because the relationship between UFH dose and the ACT is unpredictable, we repeated these analyses introducing the total or weight-indexed UFH dose in the multivariable model. For the total dose, there was an independent direct correlation with TIMI major or minor bleeding (OR 1.005 per 100 U, $P=0.009$). Weight was inversely correlated with bleeding (OR 0.99 per kg, $P=0.031$). As expected, advancing age, female gender, and GP IIb/IIIa inhibitors were associated with higher risk of bleeding. The model that included weight-indexed UFH dose revealed a direct relation to bleeding: OR 1.04 (95% confidence interval 1.02 to 1.07) for each additional 10 U/kg ($P=0.001$). The other independent predictors were unchanged. Interestingly, both models were mostly affected by TARGET, whereas these associations were not statistically significant in any of the other trials. At least numerically, CREDO had the highest dose of UFH and the lowest incidence of bleeding, albeit in the context of a lower rate of GP IIb/IIIa utilization.

The results did not change if only patients receiving GP IIb/IIIa inhibitors or those in whom the ACT was measured with the Hemochron device were considered.

**Discussion**

This is, to the best of our knowledge, the largest retrospective analysis of the relationship between maximum ACT during PCI and the incidence of ischemic or hemorrhagic complications. The principal findings of our analyses are that (1) despite fairly rigorous guidelines for UFH administration, the ACT varied

![Figure 1. Incidence of ischemic events at 48 hours by ACT quartiles. D indicates death.](image1)

![Figure 2. Covariate adjusted incidence of ischemic events (death, MI, or TVR) at 48 hours (with 95% confidence bands).](image2)

![Figure 3. Incidence of bleeding events by ACT quartiles. Maj indicates major.](image3)

![Figure 4. Covariate-adjusted incidence of TIMI major or minor bleeding events (with 95% confidence bands).](image4)
substantially, with nearly 100 seconds separating the first and third quartile, 22% of patients achieving ACT <250 seconds, and 21% over 360 seconds; (2) independently adjudicated ischemic complications in the first 48 hours after PCI, defined as death, MI, or TVR, did not occur more frequently in patients with lower ACT; (3) independently adjudicated hemorrhagic complications demonstrate a complex relationship to ACT, with a modestly significant increase up to 365 seconds (mainly minor bleeding) and subsequent plateau; and (4) a higher total or weight-indexed dose of UFH did not protect against ischemic events and tended, as intuitively expected, to cause more bleeding. These results, in aggregate, would suggest that higher ACTs do not confer a benefit and may even be detrimental. Equally important, it is unclear whether a minimum threshold for ACT exists in the current environment of near-universal stenting and aggressive platelet inhibition.

The explanation for the first finding is likely multifactorial. On the one hand, UFH has unpredictable biological activity despite the use of weight-adjusted dosing strategies in most patients. This contention is supported by the large variability in ACT observed in the present analysis. On the other hand, the frequent (89% overall) use of GP IIb/IIIa inhibitors in these patients may have altered the ACT, as previously demonstrated in other trials using these drugs. The lack of correlation between ACT and ischemic complications likely stems, at least in part, from the frequent pre-PCI (81% overall) use of clopidogrel, which reduces the risk for immediate thrombotic complications. The use of stents in 93% of patients likely led to superior angiographic results and to a marked reduction in residual dissections that acted as a nidus for immediate thrombosis. The absence of a constant and more powerful relation between ACT and hemorrhagic complications is more difficult to explain. Intuitively, higher ACTs would be expected to predict more bleeding. Yet, ACT is a crude and imperfect indicator of the inhibition of thrombin activity, as clearly shown with other anticoagulants. Moreover, smaller vascular sheaths and earlier sheath removal probably also contributed to the relatively low incidence of bleeding and lack of consistent correlation with ACT.

Our results are different from those observed in the analysis by Chew et al, from our institution. Among 5216 patients pooled from 6 randomized clinical trials, there appeared to be a significantly lower incidence of ischemic events among patients with ACT in the range of 350 to 375 seconds. The absolute rate of events was 50% higher than in the present analysis. The vast majority of these patients underwent balloon-only PCI, and there was no covariate adjustment across the continuum of the ACT range. Even in that analysis, the U-shaped relation between ischemic events and ACT was no longer evident in the subset (66%) treated with GP IIb/IIIa inhibitors. The bleeding rate (major or minor) was more than twice higher in the analysis by Chew et al than in the present report, which reflects the major advances in PCI over the last decade. A more contemporary group of patients analyzed at our institution, in whom stents and GP IIb/IIIa inhibitors were used in 100% and 91%, respectively, also did not demonstrate a significant correlation between ACT and ischemic or hemorrhagic complications. Similarly, Tolleson et al showed in an analysis from the Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrin Therapy (ESPRIT) trial, that death, MI, or urgent revascularization at 30 days occurred in 8%, 6.4%, and 6.6%, respectively, of the tertiles (<244 seconds, 244 to 292 seconds, and >292 seconds, respectively) of maximum pre-PCI ACT (P=NS). There was a similar lack of correlation with hemorrhagic complications.

Indeed, advances in PCI technique and pharmacology best explain the discrepancy between these series. As shown in Figure 5, when we compare patients treated with balloon angioplasty alone in the EPI trials (Evaluation of 7E3 for the Prevention of Ischemic Complications [EPIC], Evaluation in PTCA to Improve Long-term Outcome with abciximab GP IIb/IIIa blockade [EPILOG], and Evaluation of Platelet IIb/IIIa Inhibition in STENTing [EPISTENT]) with those treated with contemporary PCI in the 4 trials summarized in the present report, there has been a substantial reduction in both ischemic (P=0.03 for trend) and hemorrhagic (P<0.001 for trend) complications of PCI across a decade of clinical trials. It is remarkable how similar the median ACTs are for patients with and without events in each series.

The implications of these data are that the guidance offered by the ACT value once a modest dose of UFH (~5000 U total dose or...
60 to 90 U/kg) has been administered is of limited consequence in the setting of frequent use of clopidogrel, stents, and GP IIb/IIIa antagonists. Lower values appear to correlate with preserved efficacy and enhanced safety. As already implied in other small series, this approach appears safe and effective.\textsuperscript{8,17,18} It is unclear whether certain patients with enhanced thrombotic potential, such as those in the midst of an acute coronary syndrome or those with diabetes, would still benefit from more intense anticoagulation and monitoring. In the present analysis, neither unstable angina nor diabetes mellitus had any significant interaction with ACT in predicting ischemic or hemorrhagic complications.

**Study Limitations**

These data are obtained from randomized clinical trials, which arguably enroll low-risk patients. Despite rigorous data collection and event adjudication, ACT data were missing in 16\% of cases, which were excluded from the analysis for obvious reasons. The doses of UFH administered in REPLACE-2 and TARGET were limited to 7000 U total and 70 U/kg, respectively. As seen in the data, variations existed in the implementation of these guidelines. Inherent to such an analysis, we could not know what the ACT was at the time the event occurred or whether intra-procedural thrombotic complications led to an increased dose of UFH. Furthermore, these data reflect results in a population treated very frequently with clopidogrel and GP IIb/IIIa inhibitors and may not be applicable to a more restricted use of these agents.

**Conclusions**

With the above caveats, we conclude that in the era of frequent stent implantation and aggressive intravenous and oral platelet inhibition, peak procedural ACT after modest doses of UFH does not correlate with the frequency of ischemic complications and has a modest effect on (mostly minor) hemorrhagic complications. The weight-indexed dose of UFH correlates with bleeding complications, particularly when GP IIb/IIIa inhibitors are also administered. Additional research is needed to determine whether these results can be extrapolated to acute MI patients, to those receiving a high loading dose of thienopyridines instead of GP IIb/IIIa inhibitors, or to those undergoing PCI without stent implantation. Strict guidelines for clopidogrel therapy instead of GP IIb/IIIa inhibitors, or to those receiving a high loading dose of thienopyridine whether these results can be extrapolated to acute MI are also administered. Additional research is needed to determine the frequency of ACT measurements and appropriate levels during PCI without stent implantation. Lower values appear to correlate with preserved efficacy and enhanced safety.

**References**


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