Defining the Optimal Activated Clotting Time During Percutaneous Coronary Intervention
Aggregate Results From 6 Randomized, Controlled Trials

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Background—Unfractionated heparin has been the primary anticoagulant therapy for percutaneous coronary intervention for >20 years. Despite the availability of rapid “point of care” testing, little clinical data defining the optimal level of anticoagulation are available. Furthermore, recent reports have advocated the use of low-dose heparin regimens in the absence of large-scale, well-conducted studies to support this practice.

Methods and Results—We pooled the data from 6 randomized, controlled trials of novel adjunctive antithrombotic regimens for percutaneous coronary interventions in which unfractionated heparin constituted the control arm. Patients were divided into 25-s intervals of activated clotting times (ACTs), from <275 s to >476 s. In a total of 5216 patients, the incidence of death, myocardial infarction, or any revascularization and major or minor bleeding at 7 days were calculated for each group and compared. An ACT in the range of 350 to 375 s provided the lowest composite ischemic event rate of 6.6%, or a 34% relative risk reduction in 7-day ischemic events compared with rates observed between 171 and 295 s by quartile analysis (P=0.001).

Conclusions—Contrary to recent reports, the optimal suppression of ischemic events with unfractionated heparin therapy in patients undergoing percutaneous coronary intervention demands treatment to ACT levels that are substantially higher than currently appreciated. These data define a goal for heparin dosing within coronary interventions and establish a benchmark of optimal unfractionated heparin therapy against which future trials of novel antithrombotic regimens in percutaneous interventions can be compared. (Circulation. 2001;103:961-966.)

Key Words: heparin ■ clinical trials ■ pharmacology ■ coagulation

Since the development of percutaneous coronary intervention (PCI), intravenous unfractionated heparin has remained the primary antithrombotic therapy for the prevention of periprocedural ischemic complications.1 Adequate dosing with unfractionated heparin effectively suppresses the thrombin generation associated with balloon-induced vascular injury.2 Despite the continued evolution of antithrombotic therapies, unfractionated heparin remains an attractive option given its relatively low cost, the availability of a rapid “point of care” test for dose individualization (the activated clotting time [ACT]), and a known antagonist that allows the prompt reversal of antithrombin activity. Therefore, considering the wealth of experience associated with the clinical use of this agent, an optimal level of anticoagulation should be attainable in most patients undergoing PCI. However, defining this optimal level of ACT has been hampered by the lack of large-scale, randomized data. Current recommendations of ACT levels of 300 to 350 s are empiric3 and based on relatively small studies.4-6 Furthermore, in clinical practice, periprocedural heparin dosing varies markedly, with a recent emerging trend toward the use of lower heparin doses, despite the support of only a few small observational series.7,8 Therefore, we performed an analysis combining individual patient data from 6 randomized, controlled trials to determine the optimum range of ACT for the suppression of periprocedural ischemic events after PCI.

Methods

Trial Selection, Heparin Treatments, and ACT Measures
Trial selection was confined to studies of novel pharmacotherapies in the setting of PCI using aspirin and unfractionated heparin as the comparator arm. Routine ACT monitoring before device activation, the maximum ACT during the procedure, and 7-day follow-up documenting death, myocardial infarction (MI), urgent revascularization, and major or minor bleeding were also required for inclusion in our combined data set. Therefore, 6 randomized, controlled trials of patients undergoing PCI were available. These trials are summarized in Table 1.9-14 ACT values were drawn from the placebo arms of these studies, and a comparative analysis was also performed in the abciximab-treated patients from the Evaluation of c7E3 for the Prevention of Ischemic Complications (EPIC) trial, Evaluation in...
PTCA to Improve Long-term Outcome with abciximab Glycoprotein IIb/IIIa blockade (EPILOG) trial, Evaluation of IIb/IIIa Platelet Inhibitor for Stenting (EPISTENT) trial, and RAPPORT, Reopro and Primary PTCA Organization and Randomized Trial (RAPPORT). Each protocol targeted an ACT level $>300$ s in the control arms. The device used to assay the ACT was specified in all but 904 patients. The Hemochron assay (International Technidyne Corporation) and the HemoTec assay (HemoTec Inc) were used in 95% and 5% of patients, respectively, in whom the device used was recorded.

Among the trials, mean minimum ACT levels at device activation were similar, whereas the mean maximum ACTs varied more substantially. The minimum ACT at device activation was analyzed for patients, respectively, in whom the device used was recorded.

The minimum ACTs at or around the time of device activation were $274 \pm 108$ s, $320 \pm 74$ s, $312 \pm 89$ s, $233 \pm 85$ s, $220 \pm 110$ s, and $303 \pm 164$ s. The incidence of periprocedural ischemic events within each group was calculated. The maximum ACT during the procedure was also recorded and similarly divided, and the incidence of bleeding events was calculated for each range. Subgroup analyses were also performed for patients with diabetes and acute coronary syndromes and those receiving stents. The end point definitions for death, MI, and urgent revascularization were as defined in the individual protocols, and they were similar among the trials. The definition of bleeding endpoints for the Hirulog Angioplasty Study$^{13}$ varied substantially from the other 5 studies and, therefore, it was omitted from the bleeding analysis.

Baseline characteristics are expressed as percentages for discrete variables or as mean$\pm$SD for continuous variables. Event rates for each ACT interval were calculated as the percentage of patients experiencing an event within the specific ACT interval. Examination of event rates as quartiles of minimum ACT at device activation was also undertaken to minimize the effect of small sample sizes across some ranges of ACT. The $\chi^2$ statistic was used to compare the lowest and highest event rates in the arbitrarily determined ACT ranges and to compare event rates among the quartiles. $P \leq 0.05$ was considered significant. The Lowess smoothing function was used to generate graphic representations of the relationships between increasing ACT and outcomes.

### Results

#### Population Characteristics

In total, 6146 patients received unfractionated heparin alone and 5216 patients (85%) had ACT data available at or around the time of device activation. Maximum ACT results were available for 5444 patients (89%); however, with the Hirulog Angioplasty Study excluded, 3485 patients (64%) were used in the bleeding analysis. The demographic and procedural characteristics of all patients are presented in Table 2. Importantly, patients with acute coronary syndromes represented a substantial proportion of the population studied.

### TABLE 1. Summary of Trials

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Randomized therapy</th>
<th>Placebo arm</th>
<th>Maximum heparin dose</th>
<th>Targeted ACT, s</th>
<th>Minimum ACT at device implementation, s</th>
<th>Maximum ACT, s</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTCA</td>
<td>Abciximab 0.25 mg/kg + 0.125 g/kg/hr to 10000 U</td>
<td>Heparin bolus (10 000–12 000 U)</td>
<td>20 000 U</td>
<td>300–350</td>
<td>274±108 s</td>
<td>346±129</td>
<td>High-risk PTCA</td>
</tr>
<tr>
<td>PTCA (stent)</td>
<td>Abciximab 0.25 mg/kg + 0.125 g/kg/hr to 10000 U</td>
<td>Heparin bolus (10 000 U/kg)</td>
<td>10 000 U</td>
<td>≥300</td>
<td>320±74</td>
<td>372±134</td>
<td>All patients</td>
</tr>
<tr>
<td>Stent</td>
<td>Abciximab 0.25 mg/kg + 0.125 g/kg/hr to 10000 U</td>
<td>Heparin bolus (100 U/kg)</td>
<td>10 000 U</td>
<td>≥300</td>
<td>312±89</td>
<td>377±130</td>
<td>All patients</td>
</tr>
<tr>
<td>PTCA</td>
<td>Eptifibatide 135 μg/kg ± 0.5 or 75 μg/kg ± 0.5 g/kg/hr to 10000 U</td>
<td>Heparin bolus (100 U/kg)</td>
<td>10 000 U</td>
<td>≥300</td>
<td>233±85</td>
<td>354±147</td>
<td>High-risk PTCA</td>
</tr>
<tr>
<td>PTCA</td>
<td>Abciximab 0.25 mg/kg + 0.125 g/kg/hr to 10000 U</td>
<td>Heparin bolus (100 U/kg)</td>
<td>10 000 U</td>
<td>≥300</td>
<td>220±110</td>
<td>386±270</td>
<td>Acute MI</td>
</tr>
<tr>
<td>PTCA</td>
<td>Bivalirudin 1.0 mg/kg + 2.5 mg/kg over 4 hours</td>
<td>Heparin bolus (175 U/kg)</td>
<td>295 U/kg</td>
<td>≥300</td>
<td>303±164</td>
<td>442±179</td>
<td>Unstable angina</td>
</tr>
</tbody>
</table>

EPIC indicates Evaluation of c7E3 for the Prevention of Ischemic Complications; EPILOG, Evaluation in PTCA to Improve Long-Term Outcome with abciximab Glycoprotein IIb/IIIa blockade; EPISTENT, Evaluation of IIb/IIIa Platelet Inhibitor for Stenting; IMPACT II, Integrilin to Minimize Platelet Aggregation and Coronary Thrombosis II; and RAPPORT, Reopro and Primary PTCA Organization and Randomized Trial.
In addition, 15% of all patients received $1$ stent, and a procedural duration of $1$ hour was observed in 27% of cases.

ACT at Device Activation and Ischemic Events

The relationship between increasing ACT and ischemic events (n=5216) followed a U-shaped curve. A progressive reduction in the risk of death, MI, and urgent revascularization was observed with increasing ACT levels, as evidenced by a reduction in the composite ischemic end point from 11.1% at an ACT of 275 to 300 s to a nadir of 6.6% with an ACT of 350 to 375 s ($\chi^2$ statistic between highest event rate and lowest event rate, $P=0.026$). Beyond this level of ACT, the risk of ischemic events rises, increasing to 9.3% at ACT levels $>475$ s.

Analysis of diabetics included 1135 patients with available ACT data (83%). Correlations between the minimum ACT at device activation and ischemic events at 7 days demonstrated a similar U-shaped relationship. In comparison with the nondiabetic population and the overall population, a more pronounced reduction in ischemic events was evident between ACT levels of 350 to 375 s compared with those of 275 to 300 s in diabetic patients (Figure 3). Assessment of outcomes in the diabetic population when stratified by the same ACT ranges defined by the overall population demonstrated a 38% reduction in 7-day composite ischemic events in these ACT ranges (ACT of 171 to 295 s, 12.5%; ACT $>350$ s, 7.7%; $P=0.062$).

The relationship between ACT and 7-day ischemic outcomes among patients receiving coronary stents is derived primarily from the EPISTENT study, because stent use was restricted to bailout indications in the other studies. A total of 766 patients are included in this analysis (82%). Again, a decline in adverse ischemic events was observed with increasing levels of ACT, with lowest rates observed in the range of 350 to 375 s. In the 3203 patients enrolled with a diagnosis of unstable angina, non-Q-wave MI, evolving MI, or postinfarction angina and who had available ACT data (87%), the relationship between minimum ACT at device activation and ischemic events at 7 days resembled the overall analysis.

Concurrent Abciximab

With concurrent abciximab administration (n=4362), analysis of the 4 abciximab trials demonstrates lower ischemic event rates across the entire range of ACT values. However, in the 3458 patients with available minimum ACT data, the U-shaped relationship is no longer evident, with a plateau in the ischemic event rate of $\approx4.5\%$ at 7 days across a broad range of values (275 to 375 s; Figure 4A). Data for maximum ACT were available for a total of 3876 patients. The correlation between the maximum ACT and major and minor bleeding events demonstrated a slightly increased rate of bleeding with abciximab compared with heparin alone across the ranges of 275 to 375 s, with a substantial increase associated with ACTs beyond this level (Figure 4B).

Discussion

This analysis of individual patient data derived from the placebo arms of 6 randomized glycoprotein IIb/IIIa trials represents the largest study correlating the level of unfrac-
tionated heparin therapy and early postprocedural outcome. From these large-scale PCI trials, an optimal range of ACT for unfractionated heparin therapy of between 350 and 375 s is evident; this range is substantially higher than previously appreciated. Considering that more than two thirds of the patients within this analysis presented with an episode of coronary instability, this degree of anticoagulation seems to confer a low ischemic event rate of 6.6%, as defined by the composite end point of death, MI, or urgent revascularization at 7 days. This analysis runs contrary to the widely held clinical impression suggesting that lower dosing with unfractionated heparin is associated with equivalent clinical outcomes.

Recent reports have advocated the use of very-low-dose unfractionated heparin (2500 to 5000 U) among patients undergoing PCI. In a single-center observational study of 1375 patients receiving 5000 U of heparin before PCI, Koch and coworkers observed a relatively low rate of death, MI, or repeat revascularization of 5.4% at 48 hours. However, in addition to the shorter duration of follow-up, patients with acute coronary syndromes and those patients undergoing stenting were excluded from the analysis, and diabetics constituted only 10% of the study population. Similarly, Kaluski et al reported a 3.3% event rate for death, MI, and urgent revascularization with 2500 U of heparin before PCI after PCTA, but postprocedural creatine kinase was not routinely assayed, which likely underestimated the incidence of periprocedural MI. Vainer and colleagues performed a small trial of 404 patients randomized to either 5000 or 20 000 U of heparin before PCI. In the low-dose heparin group, only 22% of patients attained an ACT >275 s. This group had a composite event rate for death, MI, repeat revascularization, or acute occlusion of 13.2%; the rate for the high-dose group was 8% (P=NS). This lack of statistical significance has been interpreted as support for low-dose heparin regimens, although an inadequate sample size is a more likely explanation.

This current analysis refutes the notion that low-dose heparin therapy provides an efficacy similar to that of higher doses in PCI. Thus, whereas a previous trial attempting to demonstrate superior safety and efficacy with weight-individualized heparin dosing over a fixed-dosing regimen has been inconclusive, these data identify a therapeutic goal for unfractionated heparin therapy in individuals undergoing PCI. Furthermore, by increasing the therapeutic goal to >350

Figure 2. Analysis of ACT and composite ischemic event rates at 7 days as assessed in quartiles. Revasc indicates revascularization.

Figure 3. Relationship between minimum ACT at or around time of device activation and death, MI, or urgent revascularization (Revasc) at 7 days in diabetic patients. Lowess smoothing estimate and 95% confidence intervals are indicated by solid and dotted lines, respectively.

Figure 4. A. Relationship between minimum ACT at device activation and death, MI, or urgent revascularization (Revasc) at 7 days in patients receiving concurrent abciximab. B. Relationship between maximum ACT and major or minor bleeding events at 7 days in abciximab-treated patients. Lowess smoothing estimate and 95% confidence intervals are indicated by solid and dotted lines, respectively.
s, we observed a 34% relative risk reduction in ischemic events at 7 days. However, an increase in bleeding events is evident at this optimal range of ACT.

Previous authors have also attempted to define a threshold beyond which additional heparin provided no further incremental benefit. In the setting of a 186-patient, single-center, case-control study drawn from a registry of 1290 patients, Narins and coworkers\(^*\) were unable to determine a “safe threshold” for the ACT, observing an inverse relationship between ACT and ischemic events that remained linear through the observed ACT values. Likewise, Bittl et al\(^1\) reported a similar relationship in the 2039 heparin-treated patients from the randomized trial of bivalirudin in PCI.

In contrast, the present analysis demonstrates a U-shaped curve for ischemic risk, with ACT levels greater than \(\approx 400\) s associated with a greater rate of ischemic events, as observed in patients with acute MI undergoing thrombolytic therapy.\(^1\) The excess thrombotic risk observed at higher ACTs likely represents the clinical confirmation of the platelet activation observed with high doses of unfractionated heparin within in vitro models and ex vivo studies.\(^1\)–\(^2\) Interestingly, from this analysis, concurrent glycoprotein IIb/IIIa therapy seems to ameliorate the ischemic risk associated with high ACT levels, reinforcing the thrombotic pathophysiology of these events; this, again, is consistent with heparin-induced platelet activation. A similar analysis of bivalirudin therapy observed no increase in ischemic events at high levels of anticoagulation,\(^1\) possibly reflecting an absence of platelet activation observed with direct thrombin inhibitors.\(^1\)

The impact of concurrent abciximab on the ACT has been previously defined,\(^2\) and this synergy has implications for the optimal dosing of heparin in abciximab-treated patients. This meta-analysis confirms the dictum of targeting lower ACT levels when heparin and abciximab are combined, demonstrating a true inverse relationship between increasing ACT and ischemic events. Overall ischemic event rates are, as expected, reduced in comparison with heparin-only–treated patients for all levels of ACT, with a plateau across a broad range (250 to 350 s). Because the ability to inhibit thrombin generation and prolong the ACT varies among glycoprotein IIb/IIIa inhibitors, a similar relationship between heparin, ACT levels, and epifibatide or tirofiban cannot necessarily be expected; this requires formal definition.

The association between diabetes and adverse outcomes after PCI is well established. Abnormalities in baseline platelet function and coagulation may partially account for the increased risk. Complementing the previous observation that diabetics undergoing PCI benefit from higher heparin doses despite concurrent abciximab use,\(^2\) this analysis demonstrates a more prominent reduction in adverse ischemic events associated with achieving ACT levels of \(\approx 350\) s in the absence of concurrent abciximab therapy. By quartile analysis, achieving this higher ACT level provided a 38% relative risk reduction in 7-day composite ischemic events, although this reduction did not reach statistical significance due to the smaller sample size.

Beyond daily clinical practice, this meta-analysis has implications for the design of future trials investigating pharmacotherapies in PCI. Many recent studies have used heparin doses designed to achieve ACT levels that are substantially lower than those advocated by this analysis. Therefore, whether the incremental benefit over standard unfractionated heparin therapy defined by these studies would hold true with optimal heparin dosing remains uncertain. Although not the case for adjunctive abciximab therapy in the nondiabetic population,\(^1\) more aggressive heparin dosing may provide a greater suppression of ischemic events within the placebo arm, reducing the relative and absolute benefit of the investigational therapy. In future PCI trials in which aspirin, unfractionated heparin, and thienopyridines are used as the placebo-comparator arm, targeting heparin therapy to ACT levels in the range of 350 to 375 s would be required to define the true relative benefit of any novel therapy.

**Limitations**

ACT data were incomplete and, therefore, the potential for unanticipated selection biases remains. However, with such a large population, omission of data are likely to be randomly distributed across the observed ACT values. Consistent with this, analysis of demographic and procedural variables among patients without ACT data seemed similar to those in patients in whom data were available. Similarly, despite the exclusion of the Hirulog Angioplasty Study\(^1\) from bleeding outcome analysis, these results were also previously shown to correlate positively with maximum ACT but not initial ACT.\(^1\)

In addition, the specific device used to measure ACT is known to impact ACT values. For 85% of the patients, the device used to determine the ACT was recorded. When patients with ACT values recorded from the Hemochron device (95%) were analyzed separately, the range of optimal ACT remained unchanged, whereas the magnitude of difference between an ACT of 275 to 300 s and of 350 to 375 s increased marginally. As expected, an analysis of the 279 patients with ACT values recorded on the HemOTeC assay suggested optimal efficacy in the range of 300 to 325 s, which is consistent with the previously defined 28% lower readings with this device.\(^1\)

Finally, among the trials, the relationship between the ACT and ischemic events at 7 days demonstrates some heterogeneity, likely reflecting minor differences in patient populations and procedure-specific factors. Although these issues may contribute some degree of uncertainty in the absolute magnitude of benefit attainable with optimal heparin dosing, overall trends in benefit are similar among the trials. Operator-specific variations in procedural outcomes are inherent limitations of all large-scale studies involving technical procedures, both within and among trials. This limitation is somewhat mitigated by the randomized nature of each study and the availability of patient-specific data for incorporation into this analysis.

**Conclusions**

With the escalation in the cost of medical therapies, the optimization of current approaches remains as important as innovation. This meta-analysis of patient-specific data identifies an optimal level of ACT for patients undergoing PCI in the range of 350 to 375 s, a level of anticoagulation that runs...
contrary to recent clinical impressions. Furthermore, in subgroups at greater risk of thrombotic events, a steeper gradient of benefit between lower and higher levels of ACT is evident. However, this analysis also highlights the narrow therapeutic range of unfractionated heparin therapy in PCI, demonstrating the increased bleeding risk incurred when targeting maximal efficacy. Combined with the observed nonlinear relationship between the ACT level and ischemic risk, these data not only define an optimal range for individual patient therapy, but they underscore the limitations of unfractionated heparin. This analysis, therefore, delineates the benchmark of both risk and benefit with unfractionated heparin therapy and sets a standard for the development of new anticoagulant strategies.

References
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Circulation. 2001;103:961-966
doi: 10.1161/01.CIR.103.7.961

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2001 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/103/7/961

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