

Relationship of Activated Partial Thromboplastin Time to Coronary Events and Bleeding in Patients With Acute Coronary Syndromes Who Receive Heparin

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Background—Antithrombotic therapy with intravenous heparin in conjunction with aspirin reduces negative cardiovascular (CV) outcomes in patients with acute coronary syndromes. The need for a therapeutic range with the activated partial thromboplastin time (APTT) has not been validated in patients with arterial thrombosis who receive heparin. Therefore, it is unclear whether there is an association between recurrent CV events and low APTT values and between bleeding and high APTT values.

Methods and Results—We examined the relationship between the APTT and recurrent cardiovascular events and bleeding among 5058 patients with an acute coronary syndrome without ST elevation who received intravenous heparin in the OASIS-2 trial. The increase in relative risk of recurrent CV events was 1.54 (95% CI 1.10 to 2.15; $P=0.01$) among patients with APTT values <60 seconds compared with patients with APTT values ≥ 60 seconds. When patients had persistently subtherapeutic APTT values for more than 48 hours, the increase in relative risk of a recurrent CV event was 1.84 (95% CI 1.25 to 2.70). Higher APTT values were associated with bleeding; for every 10-second increase in the APTT, the probability of major bleeding was increased by 7% (95% CI 3% to 11%; $P=0.0004$).

Conclusions—In patients with acute coronary syndromes without ST elevation who are treated with intravenous heparin, our findings justify regular APTT monitoring to minimize recurrent ischemic events and bleeding. (*Circulation*. 2003; 107:2884-2888.)

Key Words: heparin ■ thrombosis ■ coronary disease

Acute coronary ischemia can present as acute myocardial infarction (MI) with ST elevation, MI without ST elevation, or unstable angina. The primary cause of acute myocardial ischemia is rupture of an atheromatous plaque in a coronary artery, which exposes a thrombogenic surface, thereby triggering thrombin generation, platelet activation, and thrombus formation.¹ Clinical trials have shown that antithrombotic therapy with heparin-related compounds, in conjunction with aspirin, reduces fatal and nonfatal cardiovascular outcomes.² Currently, the standard treatment for patients with MI without ST elevation or unstable angina is the combination of heparin and an antiplatelet agent.²⁻⁴ The activated partial thromboplastin time (APTT) is widely used to monitor the anticoagulant effect of intravenous unfractionated heparin, which is usually adjusted to achieve a predefined "therapeutic range."^{5,6} The use of a therapeutic range is derived largely from studies of patients with venous thromboembolism and is based on the belief that maintaining the APTT above a designated lower limit minimizes the risk of recurrent thrombosis, and maintaining the APTT below an upper limit minimizes bleeding.⁶ The need for a therapeutic

range for heparin has not been validated in patients with arterial thrombosis who are treated with intravenous heparin. Thus, it is unclear whether there is a significant increase in the risk of recurrent cardiovascular events among patients with subtherapeutic APTT results and a significant increase in the risk of bleeding among patients with high APTT values. If such relationships exist, it justifies the current approach of using regular APTT testing to monitor heparin in patients with arterial thrombosis. To examine the relationship of the APTT to recurrent coronary events and to bleeding in patients with acute coronary syndromes, we performed a subgroup analysis of the OASIS-2 study, a phase III trial in which 10 141 patients were randomly allocated to receive either intravenous unfractionated heparin or hirudin.⁷ Of these, 5058 patients were allocated to receive intravenous unfractionated heparin and were the subject of this investigation.

Methods

The OASIS-2 trial recruited patients with acute coronary syndromes without ST elevation from 360 clinical centers in 16 countries. Full details of the results of the main trial have been published.⁷ The

Received December 17, 2002; revision received March 25, 2003; accepted March 26, 2003.

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DOI: 10.1161/01.CIR.0000077530.53367.E9

TABLE 1. Heparin Dose-Adjustment Nomogram

Category	APTT	Action
1*	<60 seconds	Increase hourly infusion rate by 20%
2	60–100 seconds	Maintain same infusion rate and recheck APTT the next day
3*	>100 seconds	Reduce hourly infusion rate by 20%

*For categories 1 and 3, APTT is remeasured 6 to 8 hours later.

protocol was approved by the institutional review board of each hospital, and all patients gave written informed consent.

Patient Population

The eligibility criteria for the OASIS-2 study have been fully described previously.⁷ Briefly, patients were eligible if they were admitted to the hospital within 12 hours of an episode of chest pain suspected to be due to unstable angina or MI without ST-segment elevation on their admission ECG. The diagnosis of unstable angina was based on symptoms of angina that were worsening or occurred with minimal activity, associated with either current ECG evidence of ischemia or previously documented objective evidence of coronary artery disease. Patients with a history of stroke in the previous year, renal impairment (ie, creatinine >175 $\mu\text{mol/L}$ or >2.0 mg/dL), need for long-term oral anticoagulant therapy, PTCA within the last 6 months, planned thrombolysis, pregnancy, age <21 years or >85 years, body weight >100 kg, cardiogenic shock, angina not due to coronary disease, or other unrelated diseases that might limit life expectancy to <6 months were excluded.

Treatment

Eligible, consenting patients were randomly allocated to receive intravenous therapy with heparin (5000-U bolus followed by a starting infusion of 15 $\text{U} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) or hirudin (0.4 mg/kg bolus, followed by a starting infusion of 0.15 $\text{mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) in a double-blind fashion. The safety and efficacy results have been published previously.⁷ A subset of eligible patients ($n=3712$) were also randomly allocated to receive warfarin with a target international normalized ratio of 2.0 to 3.0 or standard therapy, in the presence of aspirin, and followed up for 5 months.⁸

APTT Monitoring and Infusion Adjustment

The target therapeutic range for both treatment groups was an APTT of 60 to 100 seconds. This therapeutic range was selected on the basis of the results of a study of unfractionated heparin that was performed at our institution that showed that this target range overlaps an anti-factor Xa range of 0.3 to 0.7 with most APTT reagent-coagulometer combinations.⁹ This simplified the study by accommodating the large number of APTT reagent-coagulometer combinations across the multiple centers. The dose-adjustment nomogram that was used in the OASIS pilot study ($n=909$) was also used in the present study (Table 1).¹⁰ An APTT was determined before and 6 hours after initiation of study drug; if the latter result

was within the therapeutic range, the infusion rate was left unchanged, and the APTT was measured daily thereafter. In patients whose APTT results were not in the therapeutic range, the infusion was adjusted according to the study protocol, and the APTT value was measured 6 to 8 hours later (Table 1).

Clinical Outcomes

All events in the primary and secondary efficacy composites and major safety events of the main trial were adjudicated by an independent panel of clinicians who were blinded to treatment allocation. Definitions of outcome events are given below.

Efficacy Outcomes: Recurrence

Cardiovascular (CV) death was defined as all deaths with a confirmed CV cause. New MI was confirmed if 2 of the following 3 criteria were met: (1) typical, prolonged ischemic chest pain lasting 20 minutes or more or chest pain requiring narcotic analgesia; (2) new creatine kinase (CK) enzyme increase to a level greater than twice the upper limit of the reference range (or >20% increase of the previous value if CK was already elevated), or a rise in CK-MB above the reference range; or (3) new diagnostic ECG changes.

Refractory angina was defined as a new episode of ischemic chest pain (with documented characteristic ECG changes during pain) lasting >5 minutes, occurring despite "optimal" medical treatment and requiring an additional intervention such as thrombolytic therapy, insertion of an intra-aortic balloon pump, or cardiac catheterization within 24 hours, including transfer to a tertiary care center.

Safety Outcomes: Bleeding

Bleeding episodes were classified as major (defined as clinically overt bleeding that required transfusion, surgical intervention, was life-threatening, or resulted in permanent disability) or minor (clinically overt but not meeting the criteria for major bleeding).

Statistical Methods

To assess the relationship between the APTT and recurrent ischemic events, the APTT was used as a time-dependent covariate and evaluated as a predictor of the time to a recurrent event in a proportional hazards regression model. Time from the beginning of the infusion to 72 hours was divided into 6-hour intervals, and the mean APTT within each interval was used for the analysis. As a time-dependent covariate, the APTT value just before the event was compared with the APTT value in the same time period for event-free patients. Where no measurement was taken, the value from the previous time interval was used. The same analysis was used to assess the relationship between APTT and time to bleeding events. These relationships are presented as smoothed curves. Smoothing is a nonparametric regression method, which we used to estimate the mean APTT response profile over time. A Gaussian Kernel function was used to weight the APTTs within a time window of 12 hours and arrive at a mean for that interval. This window was then moved across time to generate smoothed curves.¹¹ For the discrete variable analysis, the APTT was categorized as <60 versus ≥ 60 for recurrent events and >100 versus ≤ 100 for bleeding. Relative risks (RRs) and their corresponding 95% CIs are presented

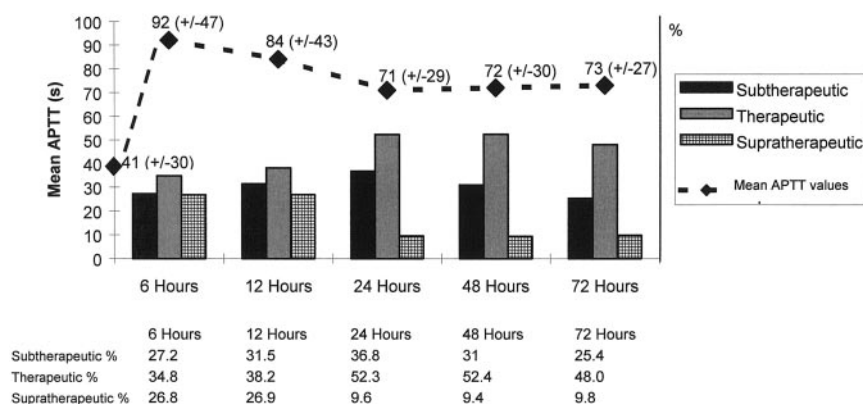


Figure 1. Mean APTT values (and SDs) and therapeutic status at selected time points.

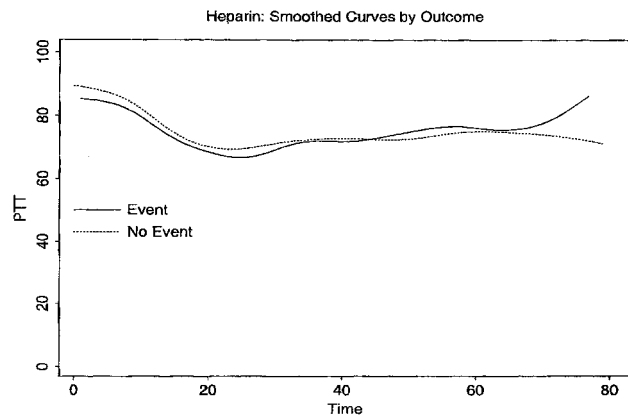


Figure 2. Smoothed curves of recurrent cardiovascular events and APTT. Outcome refers to CV death, MI, or refractory angina. No significant relationship between lower APTT values and recurrence was observed among heparin-treated patients. Time indicates hours from randomization.

from these regressions. All analyses were done with SAS version 8.0 and SPLUS version 5.0.

Results

During the study period (August 1996 to April 1, 1998), 10 141 patients were recruited; 5058 were assigned to receive intravenous unfractionated heparin, and 5083 were assigned to receive intravenous hirudin (Table 2). More than 90% (4562) of heparin patients received >48 hours of the intravenous infusion, and 80% (3994) of patients received the entire 72-hour infusion. The main reasons for early discontinuation of the intravenous infusion of heparin included the APTT being outside the therapeutic range (3.1%), an urgent revascularization or surgical procedure (2.9%), and bleeding (1.3%). The median number of dose adjustments was 2 (range 0 to 8); 44.9% of patients required both upward and downward adjustments, 33.6% of patients required an upward adjustment only, and 10% required a downward adjustment only. With these dose adjustments, the majority of patients maintained APTT values within the target range; however, the variability in APTT values was substantial (Figure 1). Among patients who had APTT values that were initially in

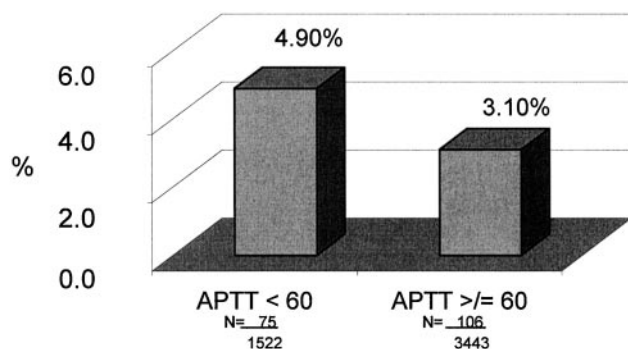


Figure 3. Recurrence rate by subtherapeutic versus therapeutic status. Hazard ratio of event (CV death, recurrent MI, or refractory angina) with last APTT value before event was 1.54 (95% CI 1.10 to 2.15; $P=0.01$ after adjustment for age, gender, body weight, smoking, diabetes, creatinine, and hemoglobin at baseline).

TABLE 2. Patients' Baseline Characteristics by Treatment Allocation

Characteristic	Heparin (n=5058)	Hirudin (n=5083)
Age, y, mean (SD)	64.0 (10.7)	64.2 (11.0)
Women, n (%)	1944 (38.4)	2015 (39.6)
Unstable angina, n (%)	4415 (87.3)	4448 (87.5)
MI without ST elevation, n (%)	627 (12.4)	621 (12.2)
Heparin before randomization, n (%)	1403 (27.7)	1459 (28.7)
Abnormal ECG, n (%)	4561 (90.2)	4616 (90.8)
Cardiac catheterization rate by day 7, n (%)	1158 (22.9)	1128 (22.2)
PTCA/CABG rate by day 7, n (%)	359 (7.1)	310 (6.1)

the therapeutic range, 77% became subtherapeutic (<60 seconds) or supratherapeutic (>100 seconds) at some point over the course of their infusion, and only 22% remained persistently in the therapeutic range. Furthermore, among patients who were initially subtherapeutic, the median time to reach the therapeutic range was 19 hours (interquartile range 10 to 41 hours), and if the first APTT was supratherapeutic, the median time to become therapeutic was 13 hours (interquartile range 7 to 23 hours). Patients who achieved therapeutic APTT results over the 72-hour infusion were more likely to be older (OR 1.01; 95% CI 1.00 to 1.02; $P=0.006$), more likely to be taking aspirin (1.52; 95% CI 1.10 to 2.11; $P=0.01$) or warfarin (1.89; 95% CI 1.42 to 2.52; $P=0.0001$), and less likely to have undergone a cardiac catheterization (OR 0.78; 95% CI 0.64 to 0.95; $P=0.01$).

Overall, there was no significant relationship between the APTT and recurrent CV death, MI, and refractory angina when the APTT was used as a continuous variable (Figure 2). However, with a cutoff of 60 seconds, the increase in RR of recurrent CV death, MI, and refractory angina was 1.54 (95% CI 1.10 to 2.15; $P=0.01$) among patients with subtherapeutic APTT values compared with patients with APTT values >60 seconds (Figure 3). Furthermore, the RR of recurrence was lower among patients who achieved progressively higher APTT targets than among patients whose APTT values were <60 seconds (Figure 4). Patients who never achieved a therapeutic APTT and hence remained persistently subtherapeutic for 48 hours and 72 hours had significantly more recurrent ischemic events than did patients who achieved therapeutic APTT results. Their RR of CV death, MI, or refractory angina was 1.84 (95% CI 1.25 to 2.70) at 48 hours and 2.21 (95% CI 1.47 to 3.31) at 72 hours (Figure 5). Persistently subtherapeutic patients tended to be younger, male, cigarette smokers, and have diabetes (Table 3).

Higher APTT values were associated with significantly more bleeding (Figure 6). For every 10-second increase in the APTT, the probability of major bleeding was increased by 7% (95% CI 3% to 11%; $P=0.0004$). When the APTT cutoff of >100 seconds was used, a significant relationship between supratherapeutic APTT values and major bleeding was observed (OR 1.48; 95% CI 1.01 to 2.17; $P=0.04$), although this became nonsignificant after adjustment for baseline factors including age, gender, weight, smoking, creatinine, and hemoglobin (OR 1.29; 95% CI 0.95 to 1.95; $P=0.22$).

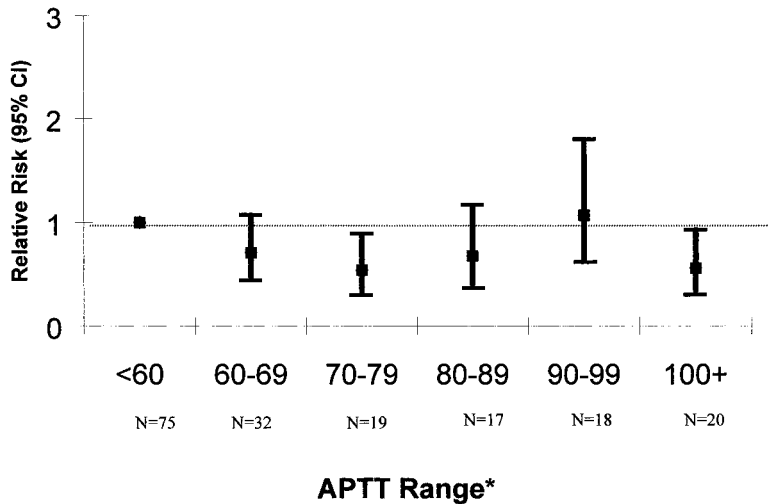


Figure 4. RR of recurrence by APTT range. Reference APTT range was <60 seconds. RRs of recurrence were lower in patients given intravenous heparin who achieved progressively higher APTT ranges (P for trend=0.06). *APTT range was determined with last APTT value drawn before CV event.

Discussion

In this analysis of patients with acute coronary ischemia who were treated with intravenous heparin, we sought to determine (1) whether there is a relationship between low APTT values and recurrent ischemic events and (2) whether there is a relationship between high APTT values and bleeding. We selected a therapeutic range for unfractionated heparin that we knew from an unpublished study (now published⁹) overlapped an anti-factor Xa range of 0.3 to 0.7 with most APTT reagent-coagulometer combinations. This information allowed us to simplify the study by accommodating the large number of APTT reagent-coagulometer combinations across the multiple centers. Dose adjustment was made with a heparin protocol that was used in the OASIS pilot study ($n=909$).¹⁰ When the APTT was examined as a continuous variable, it was not associated with recurrent CV death, MI, or refractory ischemia. However, patients who had APTT values <60 seconds were more likely to experience recurrent coronary events, and the risk of recurrence among patients who remained persistently subtherapeutic increased significantly over time. We conclude that using the clinical cutoffs to define subtherapeutic, therapeutic, and supra-therapeutic status provides the most clinically meaningful infor-

mation, because no linear ($P=0.49$) or curvilinear pattern was observed with the full range of APTT values. Given the number of infusion adjustments, variability in the timing of APTTs being drawn, and interruption of the infusion for interventional procedures, the continuous relationship between the APTT and outcomes may be obscured, because the "average" APTT per individual may not be an accurate reflection of the amount of time they spent in the therapeutic range. Although on average the APTT values of all heparin-treated patients at selected time points were within the therapeutic range, there was considerable intraindividual and interindividual variability in APTT values over the course of the infusion. Thus, as demonstrated in Figure 1, at any time point, only 50% of patients had APTT values in the therapeutic range. Furthermore, it took a long time for patients who were not initially therapeutic to become therapeutic. Finally, for those patients who were initially therapeutic, 77% of patients subsequently fell out of the therapeutic range over the course of the infusion.

For bleeding outcomes, we also observed a significant association between APTT values and bleeding, because a 10-second increase in the APTT was associated with an increased chance of bleeding of 7% ($P<0.004$) even when the

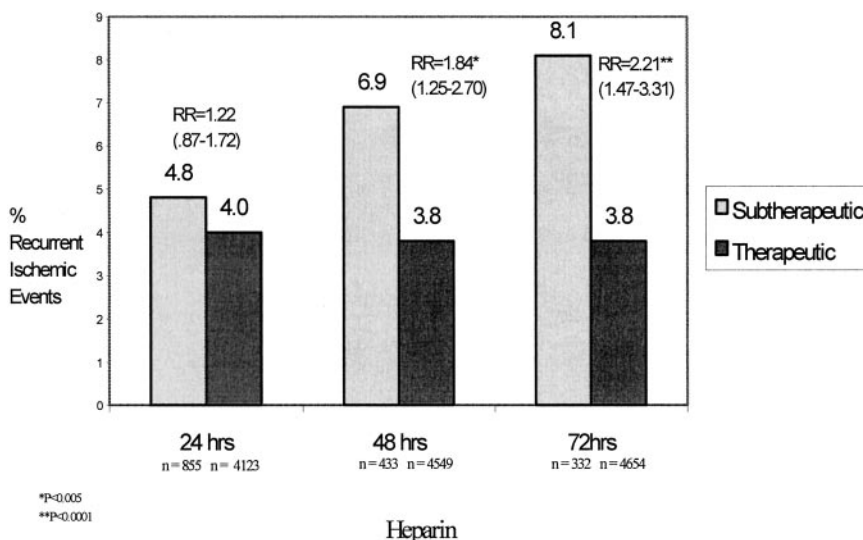


Figure 5. Persistently subtherapeutic APTT and recurrence. Persistently subtherapeutic APTT results for 48 hours or more were associated with significant increase in recurrence of CV death, MI, or refractory angina. * $P<0.005$; ** $P<0.0001$.

TABLE 3. Characteristics of Patients With Persistently Subtherapeutic APTT Results

Baseline Factors	Persistently Subtherapeutic at 48 hours (n=398)	Not Persistently Subtherapeutic (n=4590)	P
Age, y (SD)	60.3 (11.4)	64.3 (10.6)	0.0001
Male, %	70	61	0.001
BMI, kg/m ² (SD)	27.3 (5.2)	27.4 (4.5)	0.82
Current smoking, %	35.2	21.8	0.0001
Diabetes, %	31.4	20.1	0.0001
Creatinine, μ mol/L (SD)	92.1 (24.6)	92.7 (23.9)	0.68
Hemoglobin, g/L (SD)	138.2 (20.4)	136.6 (20.4)	0.12
Platelets, $\times 10^9$ /L (SD)	245.7 (69.8)	226.2 (60.6)	0.0001

BMI indicates body mass index.

APTT did not exceed 100 seconds. When the APTT cutoff of >100 seconds was used, no significant relationship between supratherapeutic APTT values and major bleeding was observed after adjustment for baseline differences in age, gender, weight, smoking, creatinine, and hemoglobin (OR 1.29; 95% CI 0.95 to 1.95; $P=0.22$). Previous studies of patients with acute coronary syndromes treated with intravenous heparin have reported that bleeding is related to elevated APTT results,^{12,13} and one study also unexpectedly found that higher APTT results were associated with an increased likelihood of recurrent ischemic events and death.¹³ However, these patients received thrombolytic therapy. We observed that in patients with acute coronary syndromes who were treated with a weight-based starting infusion of intravenous heparin in the absence of thrombolytic therapy, increasing APTT values were associated with increased major bleeding episodes, even when the APTT did not exceed the upper limit of the predetermined therapeutic range. Therefore, when the recurrence and bleeding data are interpreted together, they support the role of regular monitoring of the APTT to maximize efficacy and minimize bleeding when patients with

acute coronary syndromes are treated with intravenous heparin. Our data justify this conclusion in that once a patient becomes therapeutic, continued monitoring of the APTT is needed because a large proportion of patients subsequently fall out of the therapeutic range. Our findings suggest a lower limit of a therapeutic range of 60 seconds. The upper limit is less certain, but it should be below 100 seconds.

Study Limitations

These observational analyses were performed post hoc on data obtained from a randomized controlled trial in which one group received heparin. Therefore, caution must be exercised in interpretation of the data. However, recurrence, bleeding, and APTT parameters were defined before examination of the data, and the dose adjustments were made to maintain the APTT within a predefined range and therefore are likely to reflect a true relationship between APTT, recurrence, and bleeding.

Conclusions

Our results provide support for the use of a weight-based infusion of intravenous unfractionated heparin and justify regular APTT monitoring to maximize efficacy and minimize bleeding in patients with acute coronary syndromes without ST elevation.

Acknowledgments

Dr Anand is a recipient of a Canadian Institutes of Health Research Clinician Scientist Award. Dr Ginsberg is a recipient of a Heart and Stroke Foundation of Ontario Career Investigator Award and a Research Chair of the Canadian Institutes of Health Research/Astra-Zeneca. Dr Yusuf is a recipient of a Canadian Institutes of Health Research Career Scientist Award and holds a Heart and Stroke Foundation of Ontario Research Chair.

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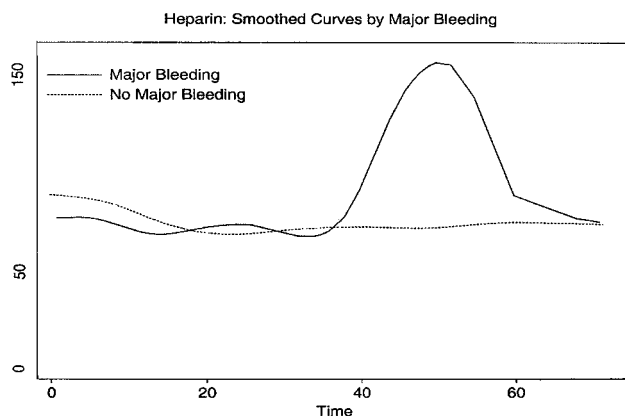


Figure 6. Smoothed curves of major bleeding and APTT. APTT values among patients who suffered major bleeding were significantly higher than for those who did not bleed. Number of people who had APTT measurements beyond 60 hours of infusion and who had major bleeding was low, which made comparisons beyond this point unreliable. Time is given in hours.