Optimal Activated Clotting Time During Percutaneous Coronary Intervention

To the Editor:

We read with interest the article by Chew et al.¹ in the February 20, 2001, issue of Circulation, but we were disappointed that such eminent investigators could confuse associations arising from heterogeneous pooled data with hard evidence on which scientific conclusions can be drawn. In their Conclusions, they state that their meta-analysis “. identifies an optimal level of ACT [activated clotting time] for patients undergoing PCI [percutaneous coronary intervention] in the range of 350 to 375 s.” Their data, however, merely show that when aiming for an ACT of 300 to 350 s, an ACT of <300 s or >475 s is a marker for increased events. It is quite possible that the level of anticoagulation has nothing to do with the increase in events.

Our conclusions from these data were that a high ACT after standard-dose heparin most likely reflects low body weight, a well-recognized cause of increased events.² Logistic regression may have helped clarify the relative importance of low body weight versus ACT in determining events in this group. Similarly, a low ACT with a standard heparin dose (heparin resistance) is a marker of systemic acute-phase response and would be associated with more actively inflamed plaques and thus a higher acute event rate, independent of anticoagulation level.

Only 85% of patients had an ACT measured, and it was <300 s in >50% of subjects. Measurement and maintenance of ACT were obviously not an important part of the study protocols. Also, non-target ACTs may have been associated with poor operators and related complications. There was also marked heterogeneity of the patient populations and heparin protocols in the different trials. The composite end points varied from 10.8% in the Evaluation of Platelet IIb/IIa Inhibitor for Stenting (EPISTENT) study³ to 17.8% in the ReoPro and Primary PTCA Organization and Randomized Trial (RAPPORT).⁴ Major bleeding rates also varied significantly, from 2.2% in EPISTENT³ to 9.5% in RAPPORT.⁴ Because the heparin regimens varied from fixed bolus² to weight-adjusted bolus with titration³ with or without postprocedural infusion,⁴ it is possible that non-target ACTs may have been more prevalent in trials with higher event rates. Any correlation between ACT and end points should have been adjusted in a multivariate manner for the trial.

In their Discussion, the authors mentioned that data from well-designed, prospective, randomized trials have contradicted the conclusions of this meta-analysis. Because of the difficulty with confounding variables, nonprospective data pooling must be regarded as inferior evidence to these trials, irrespective of the numbers involved, and cannot support changes in clinical practice.

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Response

We appreciate the response that our analysis of the activated clotting time (ACT) data from 6 large-scale randomized trials¹ has drawn. With pooled data of individual patients, the issue of heterogeneity among and within trials remains an issue for concern, particularly in trials of percutaneous coronary intervention (PCI) in which patient variables and operator variables are present. Nevertheless, the relationship between increasing ACT levels and reductions in ischemic risk was evident within each trial individually, and 7-day composite ischemic events rates were remarkably similar among the trials, in the range of 10% to 11%. The letter by Drs Hanratty and Ward erroneously cites a rate of 17.8% for the ReoPro and Primary PTCA Organization and Randomized Trial (RAPPORT), which represents the 30-day composite ischemic event rate rather than the 7-day event rate.²

Indeed, multivariate analysis had been performed in our study but was omitted in accordance with manuscript length constraints. Independent covariates of 7-day death, myocardial infarction (MI), or urgent revascularization include the following: hypertension (odds ratio, 1.29; 95% CI, 1.05 to 1.54; P=0.014), procedural duration >60 minutes (odds ratio, 2.23; 95% CI, 1.80 to 2.75; P<0.001), and the minimum ACT of 171 to 295 seconds (odds ratio, 1.39; 95% CI, 1.04 to 1.84; P=0.024). It is important to note that body weight and age were associated with adverse risk but were not independently associated on multivariate testing. In addition, on separate analysis of acute coronary syndrome patients, the relationship between greater levels of ACT and lower ischemic risk was again observed.

Thus, these data clearly demonstrate an association between an increasing ACT level and the reduction in ischemic events. We agree that causality remains an inference; however, this finding is consistent with all other available data examining the anticoagulation and ischemic outcome in PCI.³,⁴ Unfortunately, no prospective randomized data comparing ACT levels and outcome with unfractionated heparin alone during PCI exist.

In contrast to the interpretation of Drs Hanratty and Ward, the conclusions of our article do not call for a change in clinical practice but rather reinforce and reiterate the previously established recommendations for anticoagulation in PCI.⁵ Our findings argue strongly against the use of reduced anticoagulation in the absence of glycoprotein IIb/IIIa inhibition, a practice that is supported by limited, small, uncontrolled studies, often without routine assessment of periprocedural MI. Hence, “changes in clinical practice” have already
occurred, largely on the basis of clinical impression and without the support of rigorous data. If we are to use the ACT to guide anticoagulant therapy among patients undergoing PCI, then our data represent the most comprehensive attempt to address the question of anticoagulation level and outcome available.

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