Activated Clotting Time During Percutaneous Coronary Intervention: A Test for All Seasons or a Mind Tranquilizer?

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Unfractionated heparin (UFH) has been used clinically as an anticoagulant since 1935.1,2 Thirty-one years later, the activated clotting time (ACT) was developed as a test for the diagnosis and management of patients with inherited coagulation disorders.3 Later, the ACT test was extensively used to monitor UFH therapy in patients undergoing cardiopulmonary bypass surgery or percutaneous coronary interventions (PCI). Although ACT is often seen as a crude and imprecise test that does not correlate with other coagulation tests,4 it remains the most commonly used point-of-care test to monitor UFH during PCI procedures. Guidelines recommend target ACT values within 200 to 250 s with planned use of glycoprotein IIb/IIIa inhibitors and 250 to 300 s (Hemochron device) or 300 to 350 s (Hemochron device) without planned use of glycoprotein IIb/IIIa inhibitors for the guidance of UFH therapy during primary PCI procedures.5 The reference range for the target ACT is mostly empiric6 or based on small-scale studies.7–9 With regard to the association between ACT values and thrombotic or bleeding complications after PCI, studies remain markedly divided. A meta-analysis of 6 randomized trials of patients undergoing PCI by Chew et al10 showed that the risk of ischemic events reduced progressively with increasing ACT levels. The lowest rate of bleeding (8.6%) was observed in the ACT range between 325 and 350 s and it increased to 12.4% at ACT 350 to 375 s. However, this study included a heterogeneous population of the patients with a broad range of indications for PCI and only a small minority of patients received coronary stents or antiplatelet therapy (ticlopidine or clopidogrel). As a consequence, the study does not reflect the current practice of PCI. Another meta-analysis of 4 randomized trials, more contemporary in terms of the use of coronary stents or antiplatelet therapy by Brener et al11 and a post hoc analysis from the Enhanced Suppression of the Platelet IIb/IIIa Receptor With Integrilin Therapy (ESPRIT) trial12 came to opposite conclusions. Both studies did not find an association between ACT and ischemic complications in the poststenting period. A modest association between increasing ACT and bleeding events was observed either mainly driven by minor bleeding13 or enhanced by eptifibatide use.14 Thus, despite 80 years of clinical experience and almost universal acceptance of anticoagulation with UFH as a standard of care during PCI to prevent thrombotic events, the adequate UFH dosing or the relevance of monitoring of therapy with UFH by ACT remains debatable.

See Article by Ducrocq et al

In this issue of Circulation: Cardiovascular Interventions, Ducrocq et al15 assessed the relationship between the UFH dose and the peak ACT and whether there is an association between peak ACT value and thrombotic or bleeding outcomes in patients with non–ST-segment–elevation acute coronary syndromes treated by PCI. The study represents a post hoc analysis of the Fondaparinux With Unfractionated Heparin During Revascularization in Acute Coronary Syndromes (FUTURA/OASIS-8) trial.16 Patients received 2.5 mg/d fondaparinux and were randomized to low dose UFH (50 U/kg of weight) or standard dose UFH (85 U/kg of weight without or 60 U/kg of weight with planned use of glycoprotein IIb/IIIa inhibitors under ACT guidance). The study sample included 1882 patients with ACT (measured with Hemochron device) available. Approximately 80% of patients in the standard UFH arm achieved the ACT cutoff of 300 s without additional boluses of UFH compared with probably <30% in the low dose UFH arm. There was no difference in the frequency of major bleeding among patients assigned to low dose or standard dose UFH and there was a trend toward fewer ischemic events among patients assigned to standard dose of UFH. In ACT-based analyses, there was no association between ACT and frequency of bleeding either in linear or in threshold-based analyses of ACT values. With regard to thrombotic events, there was no linear relationship between ACT and thrombotic events (death myocardial infarction or target vessel revascularization) within peri-PCI (48 hours) time. However, in patients not receiving glycoprotein IIb/IIIa inhibitors, there was an increased risk of thrombotic complications for ACT values ≤300 s compared with ACT values >300 s (odds ratio of 1.78). No such an association was observed among patients who received glycoprotein IIb/IIIa inhibitors. The authors concluded that among patients with non–ST-segment–elevation acute coronary syndromes undergoing PCI, an ACT value ≤300 s was associated with increased risk of thrombotic complications; however, the ACT test did not predict peri-PCI bleeding complications.

The study by Ducrocq et al15 addresses a highly debatable issue and it may have clinical applications for the use of ACT to optimize the efficacy of UFH dosing during PCI.

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PCI procedures. In essence, the study showed that failure to achieve an ACT of 300 s or higher was associated with increased thrombotic risk after PCI. Although the study offers some contribution in this perplexed field of PCI, some caveats should be mentioned. The FUTURA/OASIS-8 trial (and consequently the current analysis) was underpowered for bleeding, as well as ischemic complications. Moreover, when analyzing the results of subgroup analyses, as was the case with multiple risk estimates for thrombotic or bleeding events calculated per 10-s increment in the ACT scale, the impact of errors introduced by multiple testing should be considered. Because of these factors, the possibility that current findings are a play of chance cannot be entirely refuted. The analysis according to ACT was not prespecified,14 and as stated in the primary publication,15 the design of the trial was not appropriate to assess whether ACT-guidance or UFH dosing was more important for preventing thrombotic or bleeding events. The lack of correlation between ACT and bleeding might have been influenced by the high proportion of patients undergoing PCI via radial approach. As recently reported, in patients undergoing coronary stenting via transradial artery approach and treated with a combination of aspirin and clopidogrel pretreatment and abciximab, greater ACT values did not correlate with increased bleeding risk.15 All patients of this study received the factor Xa inhibitor fondaparinux which is structurally related to low-molecular-weight heparins. In therapeutic concentrations, fondaparinux does not affect the ACT. Thus, one of the drugs (fondaparinux) used in all patients affects bleeding and ischemic complications without (or with minimal) interfering with ACT. Consequently, fondaparinux may have distorted the relationship between ACT and bleeding or ischemic complications in this analysis. Furthermore, the place of fondaparinux in the setting of PCI for patients with non–ST-segment–elevation acute coronary syndromes remains poorly defined.18 The drug was found to be harmful in patients with ST-segment–elevation myocardial infarction17 and current guidelines do not recommend its use in the subgroup analysis of patients without planned glycoprotein IIb/IIIa inhibitors as bailout strategy (apparently included in the subgroup analysis of patients without planned use of these agents) may further distort the ability of ACT to predict especially ischemic complications because in general glycoprotein IIb/IIIa inhibitors are used as a bailout strategy in patients considered at imminent risk of complications (mostly ischemic complications). In the FUTURA/OASIS 8 trial, low-dose UFH could not reduce bleeding but it was associated with a nonsignificant increase in ischemic complications in all patients and a significant increase among those not receiving glycoprotein IIb/IIIa inhibitors (odds ratio of 1.90).14 Apparently, a higher UFH dose alone as the standard dose used in this study had an equal (or greater) impact on ischemic complications than the ACT-guided UFH dose (compare risk estimate for ischemic complications at an ACT cutoff of 300 s), whereas bleeding was less dependent on both UFH dose and ACT guidance. Therefore, the benefit of ACT-guidance of UFH is questioned by this study. This might be even less relevant in the era of potent ADP-receptor inhibitors such as ticagrelor and prasugrel.

Teasing-out the intricate relationship between UFH dosing, ACT and thrombotic or bleeding risk during PCI remains difficult. UFH is a low-cost drug with a readily available and rapid test for dose guiding and an antagonist allowing a prompt reversal of antithrombin activity in case of drug overdosing.10 However, UFH has an unpredictable response because of marked variability in bioavailability at least partially because of variable binding of UFH to endothelial cells, monocytes, and plasma proteins.18 Unpredictable response and narrow therapeutic window necessitate dose monitoring by ACT, yet achieving anticoagulation targets has proven rather difficult and no correlation between UFH dose and ACT has been found.11,19 Even though UFH, particularly in the high doses, causes profound inhibition of coagulation cascade,20 it may be that anticoagulation with UFH alone is not sufficient to protect from thrombotic/ischemic events, such as peri-procedural myocardial infarction. In analogy, in the early days of stent implantation, coumadine therapy was associated with 3 to 4% rate of stent thrombosis despite profound anticoagulation and marked increase in the bleeding rates.21 Consequently, higher ACT values achieved by higher doses of UFH may not correlate with the propensity to vascular thrombosis. To complicate things, it has been shown that even therapeutic concentrations of UFH are associated with platelet activation by potentiating the effects of low doses of adenosine diphosphate or direct binding on platelet IIb/IIIa receptor leading to platelet activation via an outside-in signaling cascade.22 Peri-PCI antplatelet therapy represents the standard of care and since in the setting of combined therapy lower doses of UFH seem to be associated with preserved efficacy and enhanced safety, there has been a continuous reduction of UFH dosing during PCI procedures.

Contemporary PCI procedures are complex in terms of indications, combined pharmacological therapy and devices and the occurrence thrombotic or bleeding events is multifactorial and difficult to predict. Available data including the findings of the study by Ducrocq et al3 do not support ACT measurement during PCI as a reliable predictor of thrombotic or bleeding risk. This is in line with the 2014 European Society of Cardiology guidelines on myocardial revascularization that do not acknowledge a special role of ACT in the current practice of PCI.16

Disclosures
None.

References

Coronary Intervention: Aggregate Results from 6 Randomized, Controlled Trials


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