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EDITORIAL COMMENT

Activated Clotting Time During Unfractionated Heparin-Supported Coronary Intervention

Is Access Site the New Piece of the Puzzle?*

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Percutaneous coronary intervention (PCI) has developed a pivotal role in the management of patients with stable or unstable coronary artery disease (CAD). The inhibition of the coagulation cascade, and platelet activation, adhesion, and aggregation are key steps to optimize the results of PCI and prevent periprocedural ischemic complications; however, the degree of antithrombotic effect should minimize bleeding risks. Unfractionated heparin (UFH) has the main advantages of being cheap and antagonizable by means of intravenous protamine sulfate, thus it remains the most widely used anticoagulant agent during PCI. However, UFH has a poorly predictable effect on the coagulation cascade and a relatively narrow therapeutic window (1,2). Consequently, the measurement of activated clotting time (ACT) at the time of PCI has been advocated to mitigate both ischemic and bleeding events during or soon after intervention. The use of ACT was initially recommended in the mid-1970s to guide administration and reversal of UFH during cardiopulmonary bypass, then the diffusion of these interventions led to the development of automated ACT measurements (3). In 1990s, with the advances in the field of interventional cardiology, more and more cardiologists proposed to use in-laboratory bedside coagulation monitoring to assess heparin requirements during interventional procedures (3). Throughout the years, ACT monitoring to adjust UFH dosing during PCI has been promoted as the standard practice, although many centers, especially in Europe, do not assess it routinely. An intravenous UFH bolus of 70 to 100 U/kg is recommended to achieve a target ACT of 250 to 300 s (Hemotech device) or 300 to 350 (Hemochron device) without planned use of glycoprotein IIb/IIIa inhibitors (GPI) or 50 to 70 U/kg bolus to achieve an ACT of 200 to 250 s when the concomitant use of GPI is anticipated. Interestingly, no study has prospectively assessed the value of ACT-guided UFH administration as compared with standard UFH dosing, and all recommendations concerning optimal ACT values are based on retrospective and relatively underpowered registry data. What further complicates the interpretation of available data is that conflicting data have been reported on the association of ACT with ischemic or bleeding complications (**Table 1**) (4–14).

To date, a large body of evidence supports the use of transradial (TR) approach over transfemoral (TF) for PCI, particularly in acute coronary syndrome (ACS) patients, due to the lower risk of access-site-related bleeding complications and decreased mortality risk (15). However, there is limited evidence on whether the ACT target to avoid ischemic and bleeding complications should vary based on the selected access site. Interestingly, the lack of association between high ACT values and bleeding outcomes in some recent studies may be justified by the frequent use of

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TABLE 1 Main Studies Exploring the Impact of ACT on Ischemic and Bleeding Outcomes

First Author, Year, Trial	Design	Type of Patients	N	Antithrombotic Treatment	Main Findings
Ferguson et al., 1994	Observational retrospective	Stable or unstable	1,469	UFH alone	A diminished ACT response (<250 s) to an initial UFH bolus was associated with major in-hospital ischemic complications
Chew et al., 2001, EPIC, EPILOG, EPISTENT, IMPACT II, RAPPORT, HAS	Pool of 6 RCTs	Stable or unstable	5,216	UFH alone (control group of each RCT)	An ACT in the range of 350–375 s provided the lowest composite ischemic event rate in 7-day ischemic events compared with rates observed between 171–295 s by quartile analysis (p = 0.001). The maximum ACT was correlated with the incidence of major and minor bleeding (lowest rate for 325–350 s, which progressively increased with higher ACT values).
Ashby et al., 2003	Observational retrospective	Stable or unstable	1,020	UFH alone	High ACT levels were found to increase hemorrhagic complications without improving clinical or angiographic outcomes (these were paradoxically higher with increasing ACT)
Tolleson et al., 2003, ESPRIT	RCT analysis	Stable or unstable	2,064	UFH alone and UFH + eptifibatide groups	Ischemic events did not increase by decreasing ACT levels, at least to a level of 200s. Bleeding events did increase with increasing ACT levels and were enhanced with eptifibatide treatment. An ACT of 200–250 s seemed reasonable in terms of efficacy and safety.
Pinto et al., 2003, TACTICTS-TIMI 18	RCT analysis	NSTE-ACS	378	UFH + tirofiban	A peak ACT of ≤250 s was associated with higher ischemic events. A target ACT >250 was not associated with an increased risk of major or minor bleeds.
Brener et al., 2004, TARGET, CREDO, REPLACE 1 and 2	Pool of 4 RCTs	Stable or unstable	9,974	UFH + GPI (used in roughly 90%)	ACT did not correlate with ischemic complications and had a modest association with bleeding complications, driven mainly by minor bleeding. Lower values did not appear to compromise efficacy while increasing safety.
Montalescot et al., 2008, STEEPLE	RCT analysis	Stable	1,230	UFH ± GPI (roughly 40%)	Major bleeding increased significantly with an ACT >325 s. A significant relationship with increasing ischemic events was observed when ACT was <325 s indicating a narrow therapeutic window.
Bertrand et al., 2009, EASY	RCT analysis	NSTE-ACS, transradial PCI	1,234	UFH + abciximab	ACT value of >330 s were protective against peri-PCI myonecrosis, and this benefit was maintained up to 3 yrs. Greater ACT values did not correlate with an increased risk of bleeding.
Rozenman et al., 2012, HORIZONS-AMI	RCT analysis	STEMI	1,624	UFH + GPI	The peak procedural ACT achieved did not have a substantial effect on major bleeding, mortality, or MACE, although lower peak ACT was associated with less minor bleeding.
Ducrocq et al., 2015, FUTURA/OASIS-8	RCT analysis	NSTE-ACS	1,882	Fondaparinux followed by UFH (low or standard dose) ± GPI (roughly 27%)	An ACT≤300 s increased the risk of thrombotic complications in patients not receiving GPI. ACT, however, did not predict bleeding complications.
Rajpurohit et al., 2016	Observational retrospective	Stable or unstable	12,055	UFH ± GPI (roughly 55%)	After multivariable adjustment for baseline and procedural characteristics, ACT was not independently associated with in-hospital or 1-year ischemic, thrombotic, or bleeding outcomes.

ACS = acute coronary syndrome(s); ACT = activated clotting time; CREDO = Clopidogrel for the Reduction of Events During Observation; EASY = EArly Discharge after Transradial Stenting of CoronarY Arteries; EPIC = 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; ESPRIT = Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy trial; FUTURA/OASIS-8 = Fondaparinux With Unfractionated Heparin During Revascularization in Acute Coronary Syndromes; GPI = glycoprotein IIb/IIIa inhibitor; HAS = Hirudin Angioplasty Study; HORIZONS-AMI = Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction; IMPACT II = Integrilin to Minimize Platelet Aggregation and Coronary Thrombosis II; MACE = major adverse cardiovascular event(s); NSTE = non-ST-segment elevation; PCI = percutaneous coronary intervention; RAPPORT = Reopro and Primary PTCA Organization and Randomized Trial; RCT = randomized controlled trial; REPLACE 1-2 = Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events; STEEPLE = SafeTy and Efficacy of Enoxaparin in PCI patients, an internationaL randomized Evaluation; STEMI = ST-segment elevation myocardial infarction; UFH = unfractionated heparin; TARGET = Tirofiban And Reopro Give similar Efficacy outcomes Trial.

radial access site for coronary angiography and intervention (7,9).

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In this issue of *JACC: Cardiovascular Interventions*, Louis et al. (16) present the results of a large, 2-center, retrospective observational study exploring the role of ACT in patients undergoing PCI and receiving UFH alone. Overall, unadjusted and adjusted analyses showed that maximal ACT was associated with higher rates of major bleeding after TF (ACT value >290 s), but not TR PCI, whereas there was no clear association with the in-hospital ischemic risk, irrespective of the vascular access site. This finding may suggest that during TR-PCI, a more intense anticoagulation might be tolerated compared with TF-PCI as a result of a much lower access site bleeding risk in the former over the latter group of patients. This study comes from data collected in 2 American centers on 9,169 patients (mean age 66 years) who underwent PCI

without GPI. Two-thirds of the patients were male, roughly 85% presented with ACS, and the majority of them received a single-vessel PCI. Only 13% of patients received new $P2Y_{12}$ inhibitors, however.

Some important points of this study should be considered.

1. ACT values were missing in 10.5% of patients initially screened (1,532 of 14,634).
2. The ACT value at peak is analyzed as a standalone parameter, irrespective of relevant factors relating to UFH management (use of pre-PCI bolus and infusion of UFH, dose and number of intra-procedural UFH boluses, additional use of UFH doses guided by prior ACT values, patient body weight, and duration of the procedure).
3. The definition of bleeding occurrences is not standardized (i.e., BARC [Bleeding Academic Research Consortium], TIMI [Thrombolysis In Myocardial Infarction], or GUSTO [Global Use of Strategies to Open Occluded Arteries]), and bleeding events were not independently adjudicated. Moreover, the definition of periprocedural or non-procedural-related myocardial infarction is missing.
4. TR and TF cohorts were imbalanced (the TR group comprised roughly one-third of the overall population), and the TR cohort experienced a lower rate of overall bleeding complications, which were entirely driven by a lower rate of access site events. As a result, the lower statistical power to assess an association between ACT and bleeding in the TR group might explain the null finding in this group of patients. Moreover, in the TF group, the majority of bleeding events were access-related. The bottom line is that this analysis is largely underpowered to assess a possible association between non-access site bleeding and peak ACT values.
5. Hemochron device was used in all patients, thus, although this is the most widely used device, these findings should not be extended to other devices.

These findings, therefore, should be interpreted with caution and should not support the misleading conclusion that radialist operators can dose or overdose UFH liberally.

Non-access site bleeding, especially in the context of prospective randomized studies comparing TR versus TF intervention in ACS patients (7,15), is not so rare, is not influenced by the selection of the access site, and more closely correlates with mortality outcomes (17,18). On the other hand, this observation does reinforce the role of radial artery in current practice and adds to the growing body of evidence that both technical and pharmacological aspects should be regarded as highly interconnected: It is only then when the puzzle comes together!

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