Do You Always Check the ACT Before Beginning PCI?

Morton Kern, MD, with Arnold Seto, MD, MPA, VA Long Beach, Long Beach, California; Michael Ragosta, MD, University of Virginia, Charlottesville, Virginia; Mir Basir, DO, Henry Ford Hospital, Detroit, Michigan.

We were discussing a tricky thrombotic complication during a percutaneous coronary intervention (PCI). Acute stent thrombosis is a rare occurrence but in the case under review, it appears it was the result of an infiltrated intravenous (IV) line, which resulted in failure of the heparin to be delivered and hence insufficient to anticoagulate the patient. It was suggested that this complication might have been prevented if the operators had waited until they confirmed an adequate ACT (activated clotting time test). Had the ACT, which is routinely drawn shortly after heparin administration, been done, it would have been recognized as subtherapeutic.

This issue has also been addressed by the VA National Major Adverse Events Committee (VA MAEC), in response to recurrent thrombotic events and other procedural complications. The VA MAEC recommended that operators confirm that an ACT is >250 seconds (s) (normal range is 80-130s) before instrumenting a coronary artery, defined as wiring a coronary with an .014-inch guidewire. Ensuring the ACT is in the therapeutic range adds additional time (<5 minutes on average) to the procedure.

After our discussion, Dr. Seto asked:

1. Is it below the standard of care to begin an elective PCI before an ACT is returned >250s? (assume 70-100 U/kg of unfractionated heparin [UFH] has been administered). Is an ACT >200s/<250s acceptable?
2. Should an ACT >250s be required when using bivalirudin? (e.g., in case of an infiltrated IV)
3. Should the ACT >250s apply to all ACT machines? (Recall Hemochron 300-350/s [Werfen], HemoTec, Medtronic ACT Plus 250-300s, and i-STAT [Abbott Point of Care] 200-250s.)
   Undoubtedly, the time required to return an ACT is a factor for busy operators, especially for the i-STAT machine, which has become prevalent in many labs, but has the slowest time to result.
4. As an experienced operator, are you waiting for the ACT to return before proceeding?

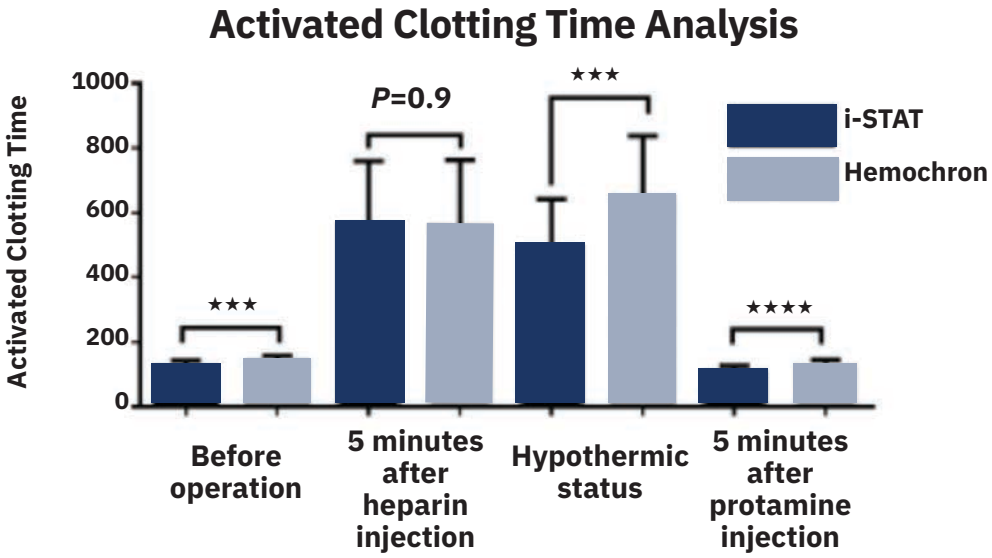

Figure 1. Comparison of ACT measurements from the Hemochron (Werfen) and i-STAT (Abbott Point of Care) at several time points before and after cardiac surgery.

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Mir Basir, DO, Henry Ford Hospital, Detroit, Michigan:

1. Is it below the standard of care (SOC) to begin an elective PCI before an ACT is returned >250s?

I do think it's below the SOC to start before an ACT is >200s. We have also had a few cases of early thrombus during elective PCI because of a poor IV.

2. Should an ACT >250s be required when using bivalirudin? (in case of an infiltrated IV, for instance).

Yes, similarly, we ask for a one-time check to make sure ACT is >300s in bivalirudin cases so we know the IV is working well. We also had a case where the IV was fine, then stopped working during a case with thrombotic complication, but I don't use a lot of bivalirudin.

3. Should the ACT >250s apply to all ACT machines? (Recall Hemochron 300-350s, Hemotec, Medtronic ACT Plus 250-300s and, i-STAT 200-250s).

I'm not sure, but that [rule] fits our model. Undoubtedly, the time required to return an ACT is a factor for busy operators, especially for the i-STAT machine, which has become prevalent in many labs, but has the slowest time to result.

4. Are you waiting for the ACT to return before proceeding?

Yes, I do wait, because we've seen the above complications in other cases. I wait until the ACT is >200s.

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.

Table. Main studies exploring impact of ACT on ischemic and bleeding outcomes.

Reprinted with permission from Valgimigli M, Gargiulo G. Activated clotting time during unfractionated heparin-supported coronary intervention: is access site the new piece of the puzzle? JACC Cardiovasc Interv. 2018 Jun 11; 11(11): 1046-1049. doi:10.1016/j.jcin.2018.02.022.

Mike Ragosta, MD, University of Virginia, Charlottesville, Virginia: Good question. At the University of Virginia, for planned PCI cases, our practice has been to confirm first with the nurse that the patient has a reliable IV, administer the heparin, proceed with guide engagement, lesion wiring, and meanwhile, draw an ACT within a few minutes of administering heparin. We use a lot of cangrelor and that is administered simultaneously with the heparin. But we don't wait for the ACT to start ballooning, etc. We don't use much bivalirudin but if we do, we do the same thing and check the ACT just to be sure [the heparin] gets in.

When radial access and a diagnostic cath are done first, we check the ACT when swapping out for a guide and before we start an intervention; usually it is therapeutic.

Arnold Seto, MD, MPA, VA Long Beach, Long Beach, California: National and international guidelines recommend an unfractionated heparin (UFH) dose of 70-100 U/kg to achieve an ACT of 250-300s for supporting PCI, (>200s when glycoprotein IIb/IIIa inhibitors are used). Understanding variable responses to and potencies of UFH, along with the risk of infiltrated IVs, etc., ACT checks are strongly recommended in American guidelines but apparently are less frequently performed in Europe. Surprisingly, though, there have been no prospective coronary studies that have assessed the value of ACT-guided dosing compared with standard UFH dosing, probably because the difference might be too infrequent to detect, or no one feels comfortable randomizing patients to such a study. Thus, all of these recommendations regarding optimal ACT ranges are based on retrospective analysis of randomized data or registry data (Table). In a prospective study of 134 non-cardiac cases, a 100 U/kg dose of UFH is sufficient to reach an ACT of >200s in 78% of patients and 41% reached >250s.[1]

I've noticed in reviewing cases both inside and outside the VA that ACTs are usually checked but not always returned prior to wiring the vessel or even starting the PCI. Undoubtedly the time required to return an ACT is a factor for busy operators, especially for the i-STAT machine, which has become prevalent in many labs. Result times average about 2-4 minutes. i-STAT device values were generally 43 seconds lower than Hemochron and 23 seconds lower than the Hepcon (Medtronic) devices. All devices correlated strongly with anti-factor Xa levels.[2]

Personally, I suspect that the anticoagulation requirement for wiring the vessel (i.e., for fractional flow reserve [FFR] only, or in preparation for PCI) is not an ACT >250s but probably lower, given the absence of disrupted endothelium and exposed tissue factor that would occur during angioplasty. As a result, in my practice, an ACT >200s where the normal ACT <120s is sufficient evidence of anticoagulation for me that (A) heparin has been effectively delivered and is working, and (B) it is safe for me to begin wiring a coronary artery for FFR or eventually for PCI while I give additional heparin to achieve ACT >250s. However, I will generally wait until the ACT is anticipated to be >250s from my additional dosing before I actually begin angioplasty and disrupting vessels, to avoid the risk of stent thrombosis.

The VA National Major Adverse Events Committee recommended that operators confirm that an ACT is >250 seconds (s) (normal range is 80-130s) before instrumenting a coronary artery, defined as wiring a coronary with an .014-inch guidewire. Ensuring the ACT is in the therapeutic range adds additional time (<5 minutes on average) to the procedure.

Mort Kern, MD, VA Long Beach, Long Beach, California: I had not been paying close attention to this issue until Dr. Seto brought it up. Our cath lab manager showed us the VA policy recommendation of waiting to have the ACT verified in therapeutic range before starting PCI. I think this is a good idea. I also think that we should not be in a hurry to begin PCI when there is preventable risk of thrombosis by checking the ACT. Repeat after me: "Safety first, especially with PCI patients". The balance of bleeding risk versus thrombosis depends on the type of procedure, concomitant medication, and patient-specific factors related to the patient's hematologic responsiveness.

When Should We Measure ACT After Bolus Dosing?

The ACT is measured approximately five to ten minutes after the initial heparin bolus, confirming we are working with a therapeutic dose. Based on the ACT, we can then adjust heparin dosage as needed. If the ACT measurement is subtherapeutic, additional boluses of UFH (e.g., 10-40 U/kg) can be administered. Our initial dose for both diagnostic and PCI cases is 5000u (about 70-100 U/kg after gaining arterial access to achieve adequate anticoagulation).

When Should We Re-Measure ACT?

Our practice is to remeasure about every 20-30 minutes, particularly for prolonged procedures. If there is evidence of a potential thrombotic complications (i.e., if a clot forms during the procedure), additional heparin is given to raise the ACT >250s.

Considerations For Altering the ACT Rules

For elective PCI cases, where potent antiplatelet agents like clopidogrel and aspirin are given beforehand, the initial ACT target can be lower. Higher bleeding risk occurs with the use of femoral access more than with the

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use of radial access. Higher ACT values are primarily associated with major bleeding in transfemoral PCI, but not in transradial PCI.

ACT Devices

The specific ACT device used can impact the ACT therapeutic range. For example, a Hemochron device will typically have a higher target range than a Hemotec or i-STAT device. Many of the established ACT cutoffs are based on older data from before the widespread use of modern stents and antiplatelet drugs. The Figure compares Hemochron and i-STAT ACT measurements at several time points before and after cardiac surgery.

Accurate ACT?

There are a few important considerations to ensure accurate ACT values. Operating teams should standardize ACT technique. Drawing from the arterial sheath side-arm versus the automated injector line can prevent large variations in the ACT results due to contamination of the sample. Avoid contamination of the blood sample when blood is drawn from an IV line that is used for heparin administration. The sample may have residual heparin, leading to a falsely elevated ACT.

Another source of ACT errors is sample mishandling. Do not let a heparinized blood sample sit for too long before testing. Platelet factor 4 (PF4) released from circulating platelets can neutralize the heparin and cause a falsely low ACT. Also recall that an ACT device can malfunction. Using an expired test cartridge can also cause ACT errors.

Lastly, because the ACT test is a global measure of whole blood coagulation, there are patient-specific conditions that can adversely affect the ACT such as hypothermia, thrombocytopenia or platelet dysfunction, or antithrombin III deficiency. Recall that since heparin binds to antithrombin III, a congenital or acquired deficiency of antithrombin can make a patient resistant to heparin and produce a falsely low ACT. Noteworthy, newer anticoagulant therapies are not accurately reflected by the ACT. This fact is particularly true for direct thrombin inhibitors (DTI), and an ACT test is not approved for monitoring these drugs.

The Bottom Line

The ACT should be in therapeutic range before disrupting a coronary artery. The rule is no guidewire insertion until ACT is in therapeutic range. While this rule applies as well to measuring FFR/nonhyperemic pressure ratio (NHPR), we often insert a pressure wire and measure FFR/NHPR to decide whether to proceed with PCI while awaiting the return of the ACT value. While not exactly the letter of the law, we try to ensure we have an ACT in range before starting the PCI part of the procedure. Rules are rules, and I think we should follow this one. ■

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