Conversations in Cardiology
Heparin Potency: What is the Right Heparin Dose for PCI in 2021?

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Our perception is that there is an increasing need for heparin dosing, which raises two questions: (1) is the heparin we use in 2020 the same potency as it was in 2019? and (2) what should be the right dose of heparin for percutaneous coronary intervention (PCI)?

Dr. Barry Uretsky of Little Rock, Arkansas, presented an issue with heparin: "One of my colleagues from Florida asked me if I've noticed a relatively ineffective heparin requiring over 10,000 units for an average case to get a therapeutic ACT [activated clotting time]. He said it has happened so often that his hospital changed vendors. He says it has continued to a great extent. I told him it has not been an issue at our hospital in Arkansas. Have you heard anything about this anywhere in the U.S.?"

In Long Beach, California, Arnold Seto and I have been seeing a requirement for higher doses of heparin requiring repetitive checking of the ACT. We are not sure if it was just a specific lot or a routine change of heparin potency. Our perception is that there is an increasing need for heparin dosing, which raises two questions: (1) is the heparin we use in 2020 the same potency as it was in 2019? and (2) what should be the right dose of heparin for percutaneous coronary intervention (PCI)?

To get some input from across the country, I sent this question to our cath lab expert group. Before seeing their responses, let's see where the issue began.

Concerns About Heparin Variability

In November 2019, a concern about subtherapeutic heparin was presented on TCTMD.[1] There were widespread reports about operators having trouble reaching adequate ACTs, reports not confirmed by the FDA. By the beginning of 2020, the problem of heparin variation was likely still ongoing and seemed to be widespread across the country with no geographic restrictions. Reports are consistently showing heparin to be weaker — and never stronger — than usual. No direct adverse events were reported as a result of inconsistent heparin at that time.

Dr. Sunil Rao, speaking to TCTMD, said nothing much has changed, except that "we are just using boatloads of heparin." On average, Rao estimated that he has approximately doubled his heparin dose per case on average since June (2019).

Now let's hear from our expert group.

Sunil Rao, Raleigh, North Carolina: [Heparin variability] was noticed widely in spring 2019. I posted a poll on social media and there was a very high response rate noticing the same thing. Medscape and TCTMD.com both did stories on it,

Table 1. Dosing of parenteral anticoagulants during PCI.

Reprinted with permission from Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *Circulation*. 2011 Dec 6; 124(23):e574-e651. doi: 10.1161/CIR.0b013e31823ba622.

Drug	Patient Has Received Prior Anticoagulant Therapy	Patient Has Not Received Prior Anticoagulant Therapy
UFH	• IV GPI planned: additional UFH as needed (e.g., 2,000 to 5,000 U) to achieve an ACT of 200 to 250 s • No IV GPI planned: additional UFH as needed (e.g., 2,000 to 5,000 U) to achieve an ACT of 250 to 300 s for HemoTec, 300 to 350 s for Hemochron	• IV GPI planned: 50 to 70 U/kg bolus to achieve an ACT of 200 to 250 s • No IV GPI planned: 70 to 100 U/kg bolus to achieve target ACT of 250 to 300 s for HemoTec, 300 to 350 s for Hemochron
Enoxaparin	• For prior treatment with enoxaparin, if the last SC dose was administered 8 to 12 h earlier or if only 1 SC dose of enoxaparin has been administered, an IV dose of 0.3 mg/kg of enoxaparin should be given. • If the last SC dose was administered within the prior 8 h, no additional enoxaparin should be given.	0.5 to 0.75 mg/kg IV bolus
Bivalirudin	For patients who have received UFH, wait 30 min, then give 0.75 mg/kg IV bolus, then 1.75 mg/kg per h IV infusion.	0.75 mg/kg bolus, 1.75 mg/kg per h IV infusion
Fondaparinux	For prior treatment with fondaparinux, administer additional IV treatment with an anticoagulant possessing anti-IIa activity, taking into account whether GPI receptor antagonists have been administered.	N/A
Argatroban	200 mcg/kg IV bolus, then 15 mcg/kg per min IV infusion	350 mcg/kg bolus, then 15 mcg/kg per min IV infusion

but the source of the problem was never found, as far as I know. It eventually just seemed to go away. We have not noticed anything lately.

David Cohen, Kansas City, Missouri: Last year, there was a fair amount of discussion around this issue on social media. Many people both in the U.S. and around the world have seen it, although the discussion has died down. There was some speculation that the underlying cause was a swine shortage in China.

Nils Johnson, Houston, Texas: As noted by others, this issue has come up several times over the past few years. A "late-breaking" American Heart Association (AHA) abstract[2] suggests that ACT is an imprecise metric. Sending simultaneous samples to two different ACT machines from the same manufacturer led to a bias of 11 with 95% confidence interval (CI) from -36 to +58, and an inter-device reliability of 30%. Thus, at least part of the problem might be imprecise ACT, and not necessarily bad heparin.

Is there another method that should be reliable over ACT? Maybe we should abandon ACT — I almost never use it. Both European and American guidelines support this point of view:

European Society of Cardiology (ESC) PCI guidelines: "Available data including the findings of the study by Ducrocq et al[3] 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."

American PCI guidelines: "... the value of the activated clotting time in current practice has been questioned ... although traditional target activated clotting time levels are included in this document, the utility of measured activated clotting time levels in current practice should be considered uncertain."

Mort Kern, Long Beach, California: Based on the responses of need for more/better heparin, it looks like doses >10,000u are common? We are still giving 5000u, checking ACT, and giving more to raise ACT >250 seconds. What are your starting and average doses of heparin?

Kreton Mavromatis, Atlanta, Georgia: We have also been requiring very large doses of heparin to achieve ACTs ~300 intermittently, often >10K U/kg. There seems to be some variability, which we have associated with changes in the brand or batch we are given. But beware of one confounding factor — the change from Hemochron (Accriva Diagnostics) to i-STAT (Abbott Laboratories) ACTs. The latter machine reads lower ACTs than the former.

Malcolm Bell, Rochester, Minnesota: Our current heparin dosing is still 70U/kg as initial dose, aiming for ACT 250-300 sec. It was often noted that ST-elevation myocardial infarctions (STEMIs) require more to keep ACT >250 sec.

Nils Johnson, Houston, Texas: Based on my reading of the guidelines (ESC does not mention ACT, American College of Cardiology (ACC)/AHA says "utility of measured [ACT] levels in current practice should be considered uncertain") and based on my "re-education" in Eindhoven, Netherlands (they never use ACT, as per ESC guidelines), I do the following:

1. Start with 100 units/kg of heparin (generally given via sheath as part of radial access that makes up most of my cases).
2. Re-bolus 5000 units after 45-60 minutes.
3. Rarely check ACT. For complex cases (chronic total occlusion [CTO], multiple wires, deep-seated GuideLiner [Teleflex], Rotablator [Boston Scientific], Impella [Abiomed]), I will check an ACT and redose heparin as needed.

Tim Henry, Cincinnati, Ohio: I give 70/kg and rarely need to give more, [to achieve] ACT frequently >400 sec.

Dave Cohen, Kansas City, Missouri: That's an important point. We did an internal validation study when we switched from Hemochron to i-STAT a few years back and found that i-STAT tended to run about 40 seconds lower than Hemochron.

Mauricio Cohen, Miami, Florida: Many hospitals forced cath labs to switch from Hemochrom to i-STAT, because of compatibility with EMRs. I personally think that the i-STAT is worse because it takes forever. I did not allow that change to happen in my lab. Curiously, I haven't found this issue lately. I did have this same issue when I practiced in Argentina a long time ago. Heparin has been a problem for a long time. Remember the late 2000s?[4]

Steve Bailey, Shreveport, Louisiana: We have similar issues in two different labs. Both labs have good outcomes and ultimately achieve a procedural ACT that is the same. Using Braun heparin and Hemochron Signature at the University Lab, our ACTs are 250-300 for **7000 units**.

At a community lab using Pfizer heparin and an i-STAT 1 300G, we are giving **14,000 units** to achieve 250-300 ACT.

Mitchell W. Krucoff, Raleigh, North Carolina: For video-densitometric ACT, any contrast media included with the sample will elevate the calculated ACT. Has anyone looked at the difference in ACTs if drawn through the guide catheter versus through a sheath or venous access? My impression is that ACT drawn via guide catheter is higher, maybe due to "contamination" with heparinized flush? I consistently have seen such different values between Duke and the Durham VA labs that I have adjusted my loading dose accordingly. Interestingly, it is less clear that we use higher intravenous (IV) rates to shift partial thromboplastin time (PTT) for deep vein thrombosis (DVT). I wonder if bolus and ACT are mechanistically different from infusion and PTT, even if heparin sources are different.

Jim Blankenship, Albuquerque, New Mexico: At Geisinger Medical Center (using an i-STAT), we gave 5000 units for radial access, then for PCI, added enough to make it 100 U/kg. That usually produced ACTs in the 250-300 range. I tried that strategy at the University of New Mexico (using a Hemochron) and that routinely produced ACT >400 sec. Now I check the ACT after 5000 units and occasionally must add more to get to 250, but not often. Acute stent thrombosis has been very rare at either institution.

Sam Butman, Cottonwood, Arizona: We give 5000-6000u with an ACT check on the Hemochron. I rarely need to give more.

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> **— Mitchell W. Krucoff, MD**

ACT Machine Differences

Lloyd Klein, Sonoma, California: I am sure everyone has read the "recipe" for heparin at one time or another. Naturally, potency will vary from time to time, because this process is not exactly scientific. Plus, there is wide individual variability in response. That is why we started doing routine ACTs in the 1980s.[5] The various ACT devices use different reagents and therefore give different therapeutic levels and are of different stability. The Hemotec ACT monitor (Medtronic) uses kaolin cartridges. The Hemochron ACT monitor uses diatomaceous earth activator. The i-STAT uses celite. The devices also measure different things. The i-STAT endpoint is indicated by a chemical measurement of the presence of thrombin instead of a mechanical measurement of a physical clot.

The old cardiovascular surgery literature suggested that fibrinolytic therapy might have a differential effect. If aprotinin is administered concomitantly, the celite activated clotting time (C-ACT) becomes significantly higher than the kaolin-activated clotting time (K-ACT). There were other studies that said that not all fibrinolytic agents had a differential effect. There is good correlation between ACT results from each. But the i-STAT ACT-K cartridge is reported to perform with better precision and reproducibility than the Hemochron. Activated clotting time has no relationship to any standard thrombosis measure.

The Bottom Line

Although ACT is often seen as a crude and imprecise test that does not correlate with other coagulation tests,[6] it remains the most used point-of-care test to monitor unfractionated heparin (UFH) during PCI procedures. U.S. guidelines recommend target ACT values within 200 to 250 sec with planned use of glycoprotein IIb/IIIa inhibitors, and 250 to 300 sec (Hemotech) or 300 to 350 sec (Hemochron) without planned use of glycoprotein IIb/IIIa inhibitors for the guidance of UFH therapy during primary PCI procedures.[7] However, we should acknowledge that the utility of measured activated clotting time levels in current practice should be considered uncertain.

From my review of our practices, the starting heparin dose for radial catheterizations and PCI cases is still 5000-7000u IV with an ACT check within 10 minutes and a recheck every 30 minutes to keep ACT >250 sec. ■

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