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Editorial

Of Hammers, Nails, and our Ever-Expanding Box of Tools...

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John F. Canales[1], James J. Ferguson[1]

"When you are swinging a hammer, everything looks like a nail."

This bit of folk wisdom is something that we physicians should take to heart. We have an assortment of therapeutic weaponry that we bring to bear; some of the tools we use are more favored than others, not necessarily because they are better, but frequently because they are something we have a lot of experience with, and are comfortable with. We like to use the tools (drugs, devices) that we are very familiar with, and once we have something that works well (or so we think) we tend to use it a LOT. In many ways the way we use antithrombotic therapy for coronary intervention is a perfect example of sticking with what we may be comfortable with, while we try to find ways to explore other therapeutic options and yet not straying too far from our "comfort zone".

Antithrombotic therapy is currently recommended by the American College of Cardiology, the American Heart Association, and the European Society of Cardiology for use during percutaneous coronary intervention (PCI) to prevent thrombus formation at the site of arterial injury and on coronary guide wires and catheters[1,2]. Historically, unfractionated heparin (UFH) has been the mainstay of anticoagulation therapy during PCI, however due to numerous clinical and biochemical limitations, newer antithrombotic therapies (including low molecular weight heparins, direct thrombin inhibitors, and direct and indirect Xa inhibitors) are part of an ever-expanding therapeutic armamentarium.

Low molecular weight heparins (LMWH), such as enoxaparin, have emerged as an attractive alternative to UFH for systemic anticoagulation due to the numerous biological and pharmacokinetic limitations of UFH. The inactivation of thrombin by UFH depends on the binding of antithrombin and thrombin in a chain length dependent fashion. However, most of the unwanted side effects of UFH are chain length (and charge) dependent, including significant protein binding (leading to inconsistent bioavailability with unreliable and variable degrees of anticoagulation), significant platelet activation, the risk of heparin-induced thrombocytopenia, and the inability to block clot bound thrombin[3-5].

Although LMWH (administered subcutaneously) is already established as an integral part in the modern-day medical treatment of ACS, the use of LMWH as an alternative anticoagulant for procedural use during elective (or urgent) PCI is less well established. A number of studies have examined the use of intravenous enoxaparin as an alternative to UFH in elective PCI[6-9]. In these relatively small studies, LMWH, administered intravenously instead of subcutaneously, in the non-emergent procedural PCI setting was as efficacious as UFH, with similar bleeding risk. The STEEPLE trial[10] is the most recent large scale prospective study comparing UFH with IV enoxaparin in elective PCI.

In the STEEPLE trial[10], 3,528 patients were randomized to IV enoxaparin (0.5 mg/kg or 0.75 mg/kg) or IV UFH (50-70 U/kg or 70-100 U/kg) with or without a GP IIb IIIa antagonist. The primary endpoint, non-CABG-related major plus minor bleeding at 48 hours occurred in 6%, 6.6%, and 8.7% of the 0.5 mg/kg IV enoxaparin group, 0.75 mg/kg IV enoxaparin group, and IV UFH group ($p = 0.014$ for 0.5 mg/kg enoxaparin vs. UFH, and $p = 0.052$ for 0.75 mg/kg enoxaparin vs. UFH). There was no statistically significant difference in death, non-fatal MI, or urgent target vessel revascularization at 30 days. By multivariate analysis, assignment to the enoxaparin group was an independent predictor of reduced major plus minor bleeding. Despite the additional safety information that STEEPLE[10] provided regarding procedural IV enoxaparin, a number of questions still remain unanswered, including long-term outcomes, optimal dosing, and the extent and clinical significance of anti-Xa inhibition achieved.

[1] Texas Heart Institute at St. Luke's Episcopal Hospital - Houston, Texas, USA.
Correspondence: John F. Canales. Texas Heart Institute at St. Luke's Episcopal Hospital, 6720 Bertner, M/C 1-133 Houston, TX 77030 - USA
E-mail: jcanales1@sleh.com
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In the current issue of ***Revista Brasileira de Cardiologia Invasiva***, Centemero et al.[11] provide additional insight into the safety and efficacy of IV enoxaparin in elective PCI. The authors describe their single center, prospective, open label, observational experience with consecutive patients receiving IV enoxaparin (0.75 mg/kg; n = 57) for elective PCI, in comparison to their experience with IV UFH (100 IU/kg; n = 143) in similar patients. PCI was performed in the setting of oral aspirin and thienopyridine therapy (without specific clarification of glycoprotein IIb/IIIa inhibitor use). Anti-Xa levels were measured 10 minutes after the bolus dose of intravenous enoxaparin and at the end of the procedure; activated clotting times and anti-Xa levels in the UFH comparison group were not reported. Patients were followed for the primary outcomes of TIMI major/minor bleeding and major cardiovascular events (death, AMI, stroke, emergency revascularization) during hospitalization, there were no significant differences in primary outcome endpoint in this relatively low risk population Patients were subsequently followed up for 3 years following PCI, with a secondary composite outcome of death, AMI, stroke, and repeat revascularization; at 3 years, there were also no differences between groups in major cardiovascular events. Anti-Xa levels 10 minutes after the IV bolus were 1.21 ± 0.23 IU/ml (range 0.73-1.68 IU/mL), and 1.04 + 0.23 IU/ml at the end of the procedure (range 0.56 to 1.61 IU/ml) after the procedure. There were no analyses performed to explore potential relationships between anti-Xa levels and outcomes, and no close characterization of the onset and offset of anti-Xa activity.

Several aspects of this study deserve comment. This study was a relatively small observational study performed at a single hospital in a low to moderately complex patient population presenting for elective PCI. Little in the way of detail on further adjunctive therapy (or the extent of anticoagulation in the comparator group) are provided. Other than documenting anti-Xa activity in the enoxaparin group (itself a valuable contribution) there were no subsequent analyses of the degree of anticoagulation with either UFH or enoxaparin, or it's linkage to outcomes. There are indeed opportunities to perhaps learn even more.

With regards to the safety of IV enoxaparin (0.75 mg/kg), there were no TIMI major bleeding events, and 5 TIMI minor bleeding events in both the UFH and IV enoxaparin groups (3.5% vs. 8.8%, p = 0.15). Although not statistically significant, bleeding events tended to be higher in the IV enoxaparin group than UFH, in contrast to STEEPLE[10], which showed lower bleeding rates with enoxaparin. The authors used UFH "controls", dosed at 100 U/kg, but did not mention ACT dosing guidelines (if any) or report the use of additional supplemental UFH. The anti-Xa activity in the present study was measured with an assay that appears different from one used by STEEPLE investigators, so cross-trial comparisons are not meaningful. Currently there is uncertainty about the preferred "therapeutic range" for anti-Xa activity in procedural LMWH use. Previous trials have suggested reduced cardiovascular events with anti-Xa levels > 0.5 IU/mL, but this target range is largely drawn from the DVT treatment/prophylaxis literature, and cannot and should not be extrapolated to arterial thrombotic processes, which may have completely different mechanistic underpinnings. Probably the most valuable information from this study lies in the distribution curves in Figure 1.

Lastly, 36% of the study population had elective PCI in the setting of an "unstable clinical presentation"; 21.5% were reported to have NSTE ACS (though presumably without dynamic ECG changes or positive biomarkers as reported in the exclusion criteria). It is unknown whether patients in the acute setting were given other anticoagulants ("cross-over" or "stacking") or antiplatelet agents (glycoprotein IIb/IIIa inhibitors) before elective PCI. As we know from SYNERGY[12] trial, adding UFH to enoxaparin in an uncontrolled fashion ("stacking" therapy), as opposed to a controlled, protocol-driven transition, may lead to an increase in bleeding complications.

In regards to the efficacy data, Centemero et al.[11] describe the major cardiovascular events during hospitalization and at 3 year follow up. Major cardiovascular events were recorded during hospitalization without mention of how long patients remained in the hospital nor at what time point outcomes were measured. There were no statistically significant differences between UFH and enoxaparin during hospitalization (zero clinical events). The incidence of CKMB elevated > 3 times the normal limit was observed in two cases in the enoxaparin group without further details of specific anatomy or events. Obviously with such small sample sizes there is virtually no statistical power to detect differences in very infrequent events. At three year followup a number of additional events had occurred in the two groups, with no sigficant differences between groups (35 vs. 18 in enoxaparin group, p = 0.47).

A final point worth noting is the emerging appreciation of differences in the pharmacodynamic activity of enoxaparin when it is given intravenously versus when it is given subcutaneously. In contrast to the generally-held clinical view that ACTs and aPTTs are not useful for monitoring LMWH, numerous studies have shown that when given intravenously, LMWH (both enoxaparin and dalteparin) do significantly affect both the ACT and the aPTT. However, in other studies of subcutaneous LMWH use, no such changes are noted. Why could this be? One potential resolution to this conundrum is the working hypothesis that subcutaneous LMWH may have significantly less absolute anti-IIa activity (perhaps relating to the avid protein binding of longer heparin chains in the tissues), and little-to-no-effect on the ACT and the aPTT, while

with intravenous use there is less "filtering" of the anti-IIa activity, and commensurately greater anti-IIa effects. In essence, they two different routes of administration may give you the equivalent of two totally different pharmacologic agents. Given the importance of inhibiting thrombin activity (anti-IIa effects) in the physiologic milieu of PCI, a much better understanding of the pharmacodynamic effects of intravenous LMWH is necessary. We already know that the pharmacokinetics (onset/offset) of intravenous LMWH are much closer to that of IV UFH – it may be that the pharmacodynamics (Xa/IIa effect) are also much closer to one another than to subcutaneous LMWH. For now, this remains a hypothesis, but one with profound clinical implications.

In summary, while the study by Centemero et al.[11] does not give definitive answers on the safety and efficacy of IV enoxaparin in elective PCI, it does provide valuable incremental information, especially about anti-Xa activity following IV bolus enoxaparin. Previous studies, including STEEPLE, have shown that IV enoxaparin can be safely given to low risk patients undergoing elective PCI. The current study corraborates this and provides new longer-term follow-up, albeit in a limite number of patients. More data exploring procedural outcomes in relation to the degree of anticoagulation, better characterization of the rise and fall of anti-Xa activity, and larger numbers of patients that allow valid analysis of clinical subsets and concomitant antiplatelet therapy will be helpful in the future.

We are moving beyond the one-trick world of hammers, and as our box of tools expands, we must remember, above all else, that it is not only just the tools we need to worry about, but the skill and experience of the person using those tools that makes the difference between a good operator and a truly masterful one. One size does not fit all for interventional cardiology, and, with time, we will come to better appreciate the clinical nuaces of where tools like intravenous enoxaparin may be best employed. We still have a lot to learn.

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