Editorial

# An evidence-based standardized protocol for anticoagulation following congenital heart surgery

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Unfractionated heparin is the cornerstone of prevention and treatment of thrombosis in children undergoing cardiac surgery due to its short half-life and reversibility using protamine. Yet, optimal titration in children remains challenging (1). Age-related differences in heparin clearance (2), protein binding activity (3,4) and anti-thrombin concentration (5-8), which are most pronounced in neonates and young infants, obscure the applicability of standard adult dosing protocols. Furthermore, responses to common monitoring tests, such as the activated partial thromboplastin time (aPTT) and the anti-factor Xa assay, also vary according to developmental stages (9,10) and illnesses (11,12). For a given level of ant-factor Xa, it is typical for the aPTT to be higher in children than adults (13). A poor correlation between aPTT and anti-factor Xa levels has previously been reported in young infants (14,15). It is, therefore, sensible to question the validity of currently used nomograms.

At the Boston Children's Hospital, Nair and colleagues took great care to create and implement an anticoagulation protocol for infants and children after congenital heart surgery. The protocol, along with their early experience, was published in a recent issue of *The Journal of Thoracic and Cardiovascular Surgery* (16). The protocol was the fruit of an extensive systematic review combined with the expert opinion of a multidisciplinary team involving hematologists, cardiac surgeons, intensivists, and specialists in laboratory medicine. Patients in whom anticoagulation was indicated were managed according to an algorithm to titrate unfractionated heparin that considered both aPTT and anti-factor Xa levels. The titration matrix was intended to rely on anti-Xa levels when possible, while using an aPTT limit (100 seconds) to prevent extreme doses that could increase bleeding risks. In the delicate balance between thromboembolic and bleeding events, the rationale was to identify a strategy that would minimize bleeding without increasing thrombosis.

Implementing the Boston Children's Hospital anticoagulation protocol involved a concerted effort with educational sessions, placards at every bedside and work area containing the protocol and investigator phone number, and daily rounding by study members with medical teams to provide clarifications and address questions. Implementation was performed as part of a wider institutional initiative aimed at standardizing anticoagulation therapy in all cardiac patients (17,18). In addition to regulating practice, the authors prospectively assessed outcomes. A cross-sectional analysis was performed comparing bleeding complications, thromboembolic events, and treatment adherence over a 5-month period prior to (N=87) and after (N=116) protocol implementation (16).

In a multivariate model that adjusted for age and Risk Assessment for Congenital Heart Surgery (RACHS) score, the protocol was associated with a lower incidence of clinically relevant bleeds [risk ratio (RR) 0.39, P=0.006], with no significant difference in major hemorrhages (16).

Although the study was underpowered to compare thromboembolic events, no signal for an increased risk was detected, with a direction of effect favoring the standardized protocol (RR 0.76, P=0.55). The protocol was associated with less time spent below the therapeutic range, albeit at the expense of more frequent blood draws and dose adjustments. Compliance with protocol titration recommendations was 87%.

Naturally, there are numerous challenges to observational research. Patients were not randomized to a protocol-driven approach versus usual care. While analyses adjusted for two important factors (age and RACHS score), unknown or unmeasured potential confounders could not be taken into consideration and the number of variables controlled for was limited by the event rates. The pre-protocol phase could be contaminated by education leading to protocol implementation, which may produce a bias towards the null hypothesis, potentially resulting in an underestimation of the benefits of the standardized approach. Moreover, the lack of blinding can result in a Hawthorne effect that is difficult to exclude, with caregivers modifying their behavior as a result of being under observation. Despite such inherent limitations, the study was thoughtfully and carefully executed on an important subject matter that is not conducive to a randomized controlled trial.

The Boston Children's Hospital experience serves as a shining example of improving outcomes through thoughtful standardization of care. In response to the 2008 Joint Commission's National Patient Safety Goals for Anticoagulation, an institutional decision was taken to create and implement a Cardiac Antithrombosis Management Program. Several initiatives have since demonstrated that standardized care provided according to consensus guidelines (19,20) could positively impact the clinical trajectory of even the sickest and most vulnerable patients (17,18). A few years following modification of the local care structure, quality-control initiatives swiftly demonstrated improvements in overall patient safety, family satisfaction, and adherence to best clinical practices.

In conclusion, the study by Nair *et al.* stands as a model worthy of emulation. The Boston Children's Hospital team is to be congratulated for leading such evidenced-based research that promotes standardized integrated approaches to anticoagulation in children undergoing congenital heart surgery. The investigators convincing demonstrated that adherence to carefully crafted protocols can optimize patient outcomes and create an optimal environment to assess therapies.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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