Editorial Commentary

Periprocedural anticoagulation in non-ST-segment elevation acute coronary syndrome: time to reassess?

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Non-ST-segment elevation acute coronary syndromes (NSTE-ACS) are responsible for almost 1 million admissions in the U.S. annually (1), and represent a spectrum of clinical conditions ranging from unstable angina (UA) to non-ST-segment elevation myocardial infarction (NSTEMI). The most important cause is intraluminal thrombosis due to atherosclerotic plaque rupture, which impairs distal blood flow and may lead to myocardial ischemia or infarction.

While percutaneous coronary intervention (PCI) is now the preferred revascularization strategy in most patients with stable coronary artery disease (CAD) and acute coronary syndromes (ACS), it is also associated with plaque disruption and activation of the coagulation pathway, which in turn leads to thrombin formation and platelet aggregation (2). Therefore, periprocedural anticoagulation has been widely used to reduce both short-term and long-term ischemic complications associated with the intervention (3,4). Prior clinical research on this subject was focused on avoidance of recurrent thrombotic events as well, with clinical trials that evaluated unfractionated heparin (UFH), low molecular weight heparin (LMWH) and fondaparinux showing a clinical benefit in this regard (5,6). Subsequently, these studies were crucial in shaping guideline recommendations for use of anticoagulants in patients undergoing PCI for NSTE-ACS. Nonetheless, it is important to consider that these trials were performed when the emphasis on clinically relevant bleeding and its prognostic value, routine use of dual antiplatelet therapy (DAPT), lesser thrombogenic stent platforms, and novel approaches to PCI were not the norm in practice. Therefore, the role of periprocedural anticoagulation in the modern era of PCI remains unclear.

In a recent issue of JAMA Internal Medicine, Chen *et al.* (7) sought to provide evidence on this crucial topic through an observational cohort study involving 8,197 patients who underwent PCI for NSTE-ACS between 2010 and 2014 across 5 hospitals in China. From these patients, 6,804 finally met the inclusion criteria. The primary endpoints of the analysis were in-hospital all-cause mortality and in-hospital BARC 3–5 bleeding. A propensity score analysis of 997 patients who received parenteral anticoagulation matched with an equal number of patients who did not was also conducted. About one-third of the included patients received periprocedural anticoagulation and 97% received DAPT. Of note, there were no differences observed in the in-hospital endpoints of mortality and myocardial infarction (MI) between the two groups, however, the incidence of in-hospital BARC 3–5 bleeding was significantly higher in the group that received parenteral anticoagulation. Similar findings were reflected in the long-term follow-up of these patients as well as the propensity score analysis.

The authors must be commended for this well-conducted study that attempts to address a knowledge gap in this ever-

evolving field. The analysis highlights that with PCI and its associated protocol now being widely followed to prevent ischemic events, the protective effect of periprocedural anticoagulation has come into question. Interestingly, while the finding of similar rates of mortality between the groups was consistent throughout follow-up, the differences in long-term major bleeding rates were primarily due to more bleeding episodes within the first 30 days of the procedure in the periprocedural anticoagulation group. This suggests that the difference in bleeding was, in fact, driven by the periprocedural management of these patients and not by the imbalance in baseline characteristics.

However, despite the intriguing results, one must examine these findings in the context of a broader clinical picture. Only a low percentage of patients in the study received fondaparinux or other newer anticoagulants that have been associated with lower bleeding rates; a limitation the authors acknowledge might have underestimated the efficacy of periprocedural anticoagulation. Although mortality and MI as ischemic endpoints were analyzed, stent thrombosis, an important device-related complication that is certainly influenced by periprocedural management, was not evaluated in the present report. Another critical aspect that must be discussed is antiplatelet therapy, which is now at the core of medical management in patients presenting with ACS. With the incorporation of more potent $P2Y_{12}$ inhibitors in DAPT regimens, especially for high-risk patients (8), the role of anticoagulation is being further diminished. Finally, the emergence of cangrelor, a short-acting intravenous $P2Y_{12}$ inhibitor, as a potential bridging agent will prompt reconsideration of the optimal strategy for periprocedural management during PCI (9).

In summary, the study by Chen et al represents a clinically relevant contribution and raises some valid questions on the value of periprocedural anticoagulation in NSTE-ACS patients undergoing contemporary PCI. However, since the absence of evidence is not the evidence of absence, results from this observational cohort study must be considered hypothesis generating. A randomized trial to address this issue is long overdue and is certainly needed to provide the highest quality of care to this high-risk subgroup of patients. All factors considered, physicians must take the risk of major bleeding into account in NSTE-ACS patients requiring anticoagulation and DAPT.

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Footnote

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