To the Editor:

We read with interest the expert review\(^1\) by Dr. Waterford and Dr. Ad summarizing key aspects of nonvitamin K oral anticoagu-
ulants (NOACs) as they relate to patients undergoing cardiac surgery. Their review was thorough, highlighting several key considerations for the management of NOACs in the perioperative period. The discussion briefly touched on reversal agents; however, this area warrants further conversation, as there are emerging data to suggest that andexanet alfa, a targeted reversal agent for factor Xa inhibitors (apixaban, rivaroxaban, and edoxaban), should not be used for emergent reversal before cardio-
pulmonary bypass (CPB).\(^2,3\)

Pharmacologically, andexanet alfa is a recombinant factor Xa decoy that impacts several aspects of the coagulation cascade. Notably, as a factor Xa decoy, it binds to antithrombin III, reducing the circulating antithrombin III–heparin complexes, which renders heparin ineffective.\(^4\) As evidenced by an increasing number of case reports, the competition between heparin and andexanet alfa for heparin binding manifests as heparin resistance.\(^5,8\) This heparin resistance was first reported in 2019 with the publication of a case of a ruptured abdominal aortic aneurysm where therapeutic activated clotting time could not be achieved during endovascular repair.\(^5\) In the cardiac surgery literature, 2 cases have been published purporting the “safe” use of andexanet alfa in the perioperative setting.\(^3,5\) While no specific thrombotic adverse event was reported, these cases further illustrate the risks associated with andexanet alfa–induced heparin resistance and the challenges with maintaining anticoagulation before and during CPB. Our group has found that the risks associated with heparin resistance and thrombus formation during CPB preclude the safe use of andexanet alfa before urgent or emergent cardiac surgery and recommend against it (Brenner B, Guerra J, Williams C, Littlewood K, Kern J, Tanaka K, et al, personal communication, 2022). In a forthcoming case series, currently under review, our group experienced the significant heparin resistance after andexanet alfa administration in the pre-CPB period. This, in conjunction with the administration of prothrombin complex concentrates, also led to pump thrombosis, requiring emergent pump exchange during deep hypothermic circulatory arrest for the repair of a type A dissection. Fortunately, this patient did well without any adverse effects. Finally, regulatory bodies in Europe have taken note of these reports and issued a direct health care professional communication disseminated in November 2020 recommending against the use of andexanet alfa before heparinization.\(^9,10\)

Based on the mechanism of action of andexanet alfa and the evolving case reports of heparin resistance and thrombosis during CPB, use of andexanet alfa should be avoided in the perioperative period in patients requiring urgent or emergent cardiac surgery. Importantly, the 2021 Society of Thoracic Surgeons–endorsed clinical practice guideline on blood management recommends the use of andexanet alfa for patients in need of emergent cardiac surgery.\(^11\) There is an urgent need to update these guidelines, given these emerging data. If at all possible, surgery should be delayed, allowing for the natural clearance of the NOAC. In emergent cardiac surgery, for patients on an NOAC, consider the institution of heparin-based anticoagulation without prebypass reversal of the NOAC followed by rotational thromboelasto-
metry and directed correction of coagulopathy with pro-
thrombin complex concentrates following CPB. For the patient who has received andexanet alfa, either at an outside institution, or in the case of an unanticipated need for CPB, supplementation with antithrombin has been shown to be a potentially viable strategy.\(^5\) Alternatively, one could consider the use of bivalirudin for CPB, given its different mechanism of action; however, as far as we are aware, the use of bivaliru-
din in this setting has not been established.

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New Avenues

Reply to the Editor:

We enjoyed reading Beller and colleagues’ response to our editorial entitled “Nonvitamin K oral anticoagulants in cardiac surgery: What cardiothoracic surgeons need to know 2.0.” We in particular look forward to reading more on this in future publications. We are not certain that use of bivalirudin represents a prudent alternative to heparin in patients on DOACs that have not been reversed before cardiac surgery. While use of direct thrombin inhibitors are mandatory in cases of acute heparin-induced thrombocytopenia, the lack of reversal agent for bivalirudin might lead to increased bleeding, especially when bivalirudin is combined with a DOAC. Although some studies (such as EVOLUTION-ON [The Evaluation of Patients During Coronary Artery Bypass Graft Operation: Linking Utilization of Bivalirudin to Improved Outcomes and New Anticoagulant Strategies]) suggest no increased bleeding with bivalirudin, others (such as CHOOSE-ON [Coronary Artery Bypass Grafting: Heparin-Induced Thrombocytopenia Thrombosis Syndrome On- and Off-Pump Safety and Efficacy]) suggest quite high rates of transfusion with bivalirudin, and there are no studies that combine bivalirudin administration with DOACs. What has become clear is that DOAC use is on a significant rise, and cardiac surgeons will be faced with the prospect of emergency cases concerning patients on DOACs, and that more data are urgently needed to better guide practice.

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References