To the Editor.—In an article, published in the May 2015 edition of Archives of Pathology & Laboratory Medicine, the efficacy, methods of laboratory monitoring, and approach to emergent “reversal” of warfarin, dabigatran, rivaroxaban, and apixaban were discussed. However, a third direct factor Xa inhibitor, edoxaban, was recently approved by the US Food and Drug Administration to (1) protect against systemic embolism and stroke in patients with nonvalvular atrial fibrillation, and (2) treat deep vein thrombosis and pulmonary embolism. Because this is likely to become an equally popular form of anticoagulation, it is important to provide an update to that original article to summarize the efficacy, methods of laboratory monitoring, and approach to emergent “reversal” of edoxaban.

Similar to rivaroxaban and apixaban, edoxaban is an oral, direct inhibitor of factor Xa. It is typically administered once daily at a 30- or 60-mg dose, depending on the creatinine clearance of the recipient. The ENGAGE AF-TIMI 48 study—a randomized, double-blind clinical trial—reported that the incidence of stroke or systemic embolism in patients with nonvalvular atrial fibrillation taking edoxaban was noninferior to warfarin therapy. Less overall bleeding and a reduction in cardiac death was reported in patients taking edoxaban. Patients with nonvalvular atrial fibrillation and a creatinine clearance greater than 95 mL/min should not be treated with edoxaban because they are more likely to suffer from thromboembolic disease compared with similar patients taking warfarin. The Hokusai-VTE study—also a randomized, double-blind clinical trial—reported that treatment with edoxaban was noninferior to treatment with warfarin for the prevention of recurrent, symptomatic thromboembolism. Treatment with edoxaban was associated with significantly less bleeding than treatment with warfarin.

As with the other factor Xa inhibitors, therapeutic monitoring is not required during routine treatment with edoxaban. In an emergent situation, obtaining standard coagulation studies (prothrombin time, partial thromboplastin time) may reveal mild prolongations, but the association between these deviations and clinical outcomes is not known. At present, there is no antidote to edoxaban available in the United States. Also, similar to other oral factor Xa inhibitors, edoxaban binds to plasma proteins and would not be expected to be efficiently removed by hemodialysis.

At our institution, we plan to address emergent “reversal” of edoxaban in the same manner as we treat emergent “reversal” for the other factor Xa inhibitors: a one-time, off-label dose of 25 units/kg of the 4-factor prothrombin complex concentrate, with a dose not to exceed 2500 units total. To be clear, this approach is only intended for patients with life-threatening hemorrhage. The rationale for this approach is limited to a phase I trial (in patients following a minimally invasive procedure and with limited bleeding), and an animal model of edoxaban-related hemorrhage. Although these studies found some benefit to providing a higher dose of 4-factor prothrombin complex concentrate than what we plan to use, patients taking edoxaban (unlike healthy study subjects or animals) are doing so because of an underlying thrombotic condition. Given the off-label nature of this indication, we feel that the 25 unit/kg dose of 4-factor prothrombin complex concentrate appropriately weighs the risk of continued, life-threatening hemorrhage against the risk of inducing catastrophic thrombosis.

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The authors have no relevant financial interest in the products or companies described in this article.

doi: 10.5858/arpa.2015-0201-LE

Who Will Do My Autopsy?

To the Editor.—As a recently retired pathology chief of a large-volume anatomic and clinical laboratory service at a community hospital, I want to applaud Dr Stephen A. Geller’s editorial letter, “Who Will Do My Autopsy?” I share his frustration and concerns with the state of autopsy pathology today, especially its underutilization. His point regarding discrepancies between the clinical diagnosis and the autopsy findings is well known, some estimates putting this figure as high as 25%. What should also be recognized is that in 10% or more of these cases medical or surgical intervention could have significantly prolonged life in these individuals.

Perhaps medicine should recall and return to its roots in the sentence written by Giovanni Morgagni on a plaque in the Anatomical Theatre in Padua, “Hic locus est ubi mors guide succurre viva” (“This is the place where death delights to serve the living”).

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doi: 10.5858/arpa.2015-0215-LE