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Dabigatran Reversal with Idarucizumab.

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and their skill level, and a possible tendency to be selected on a team to allow a more flexible strategy.[4] We speculate that players who throw right-handed and bat left-handed enjoy an additional biomechanical advantage, with the dominant (throwing) hand being placed further from the hitting end of the bat, providing a longer lever with which to hit the ball (potentially at the expense of bat control[5]). Given these sport-specific explanations, our findings argue against any advantage due to hemispheric lateralization.

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Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

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Dabigatran Reversal with Idarucizumab

TO THE EDITOR: Data provided by Pollack and colleagues (Aug. 3 issue)[1] suggest a dissociation between the normalization of the coagulation profile and the establishment of effective hemostasis after the administration of idarucizumab in patients with uncontrolled bleeding. The median time to the cessation of bleeding was 2.5 hours among patients with nonintracranial hemorrhage. In analyses reported separately, the median time to the cessation of bleeding was 3.5 hours among patients with gastrointestinal bleeding and 4.5 hours among those with nonintracranial and nongastrointestinal bleeding.[2] The median time to the cessation of bleeding was 11.4 hours when intracranial hemorrhage was included in the analysis involving patients with serious bleeding.[3] Should clinicians rely solely on idarucizumab and hope that their patients do not die from uncontrolled hemorrhage while waiting for hemostasis to be established? A reasonable approach would be to administer blood-component therapy (e.g., prothrombin complex concentrate and activated prothrombin complex concentrate) — a bridge between the normalization of the coagulation profile and the establishment of hemostasis, according to in vitro and preclinical data[4,5] — in addition to idarucizumab. It can be reasonably argued that the establishment of effective hemostasis with blood-component and idarucizumab therapy outweighs the risk of thrombotic adverse events among patients with serious hemorrhaging. The effectiveness and need for further blood-component and idarucizumab therapy may be assessed by serial clinical assessments and a serial profile of clotting times.

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TO THE EDITOR: In 2015, an interim analysis involving 51 patients with acute bleeding who had

received idarucizumab for dabigatran reversal was published in the *Journal*.[1] That article reported a median time to the cessation of bleeding of 11.4 hours among 35 of 51 patients (69%). At a 2016 American Heart Association conference, data from 298 patients with acute bleeding were presented. The median time to the cessation of bleeding was reported in 158 patients (53%) as 3.5 hours among 97 patients with gastrointestinal bleeding and as 4.5 hours among 61 patients with nongastrointestinal and nonintracranial bleeding.[2] Finally, in the full cohort analysis involving 503 patients, of the 301 patients with acute bleeding, the median time to the cessation of bleeding is reported as 2.5 hours but was analyzed in only 134 patients (45%).

We are concerned that selective reporting bias influenced the reporting of this important secondary clinical outcome, because each subsequent analysis reduced the fraction of the cohort included in this calculation (from 69% to 53% to 45%) while increasing the apparent clinical efficacy. We ask the authors to provide substantially more robust reporting of these data for the full cohort to better illuminate these evolving results.

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TO THE EDITOR: Pollack et al. report the anticipated final results of the RE-VERSE AD study regarding the use of idarucizumab to reverse the effects of dabigatran in patients who have life-threatening hemorrhage or who are undergoing emergency surgery. However, the authors do not report the correlation between the activated partial-thromboplastin time (aPTT) and the diluted thrombin time, the ecarin clotting time, or dabigatran concentration. There is some evidence,[1,2] and some degree of consensus,[3] that the aPTT (the only measurement available in emergency situations in most centers) is too insensitive to estimate dabigatran concentration, but little of the evidence has been gathered in the context of urgent reversal and not in a prespecified peak–trough fashion. Therefore, an analysis of this correlation in the more than 500 patients who were included in the RE-VERSE AD study would be valuable. Given that urgent reversal is a rare need, this information is not likely to be obtained otherwise. Were the aPTT results not reported or analyzed because of the already available evidence that aPTT should not be used? Would the authors provide sensitivity and specificity and predictive values for aPTT to detect therapeutic dabigatran concentrations?

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THE AUTHORS REPLY: Idarucizumab is licensed for dabigatran reversal in patients who have serious bleeding or are undergoing urgent surgery. Yip and Deng speculate that in addition to idarucizumab, prohemostatic agents such as prothrombin complex concentrate or recombinant activated factor VII should be administered to hasten hemostasis in dabigatran-treated patients with severe hemorrhage. Few of the patients who were enrolled in the RE-VERSE AD study received prohemostatic agents in addition to idarucizumab, so the efficacy and safety of such therapy cannot be assessed.[1] However, prohemostatic agents are unlikely to be of benefit unless there is associated coagulopathy, because idarucizumab reverses the anticoagulant effects of dabigatran within minutes. Furthermore, prohemostatic agents may increase the risk of thrombosis.

Radecki and DeLoughery are concerned about the divergence in the median times to the cessation of bleeding that were reported in the interim and final analyses of the data from the RE-VERSE AD study. For patients with serious bleeding, the protocol mandated the assessment of the time to the cessation of bleeding up to 24 hours after the administration of the first vial of idarucizumab.[1] The longer time that was reported in the interim analyses[2,3] reflects the inclusion of patients with recorded times exceeding 24 hours and patients with intracranial hemorrhage, many of whom did not undergo repeat brain imaging until several days after admission. To adhere to the per-protocol definition, these patients were excluded in the final analysis, which explains the shorter times to the cessation of bleeding. We agree that their exclusion limits the generalizability of the findings to this subgroup. Therefore, postmarketing data are needed to better assess the effect of idarucizumab on the time to the cessation of bleeding in these patients.[4]

Sorigue correctly points out that the diluted thrombin time or ecarin clotting time is not available in many hospitals, and he requests information on the correlation between the aPTT and these tests. This information is provided in Figure 1D of our article and in Figure S2 in the Supplementary Appendix (available with the full text of our article at NEJM.org), which show that there is good correlation between the aPTT as measured in the central laboratory and the more specialized tests. Therefore, these data provide preliminary evidence that the aPTT can also be used to monitor dabigatran reversal, provided that the test is performed with a reagent that is sensitive to the anticoagulant effects of dabigatran. In the RE-VERSE AD study, the central laboratory used the CK-Prest reagent (Diagnostica Stago). It is important to point out, however, that coagulation testing before the administration of idarucizumab is not essential in patients who have life-threatening bleeding or in whom urgent surgery is indicated.

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Since publication of their article, the authors report no further potential conflict of interest.

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IgG Endopeptidase in Highly Sensitized Patients Undergoing Transplantation

TO THE EDITOR: The study conducted by Jordan et al. (Aug. 3 issue)[1] included a low-risk population (2 patients did not have donor-specific antibodies) and pretreatment class I donor-specific antibody levels (the major risk factor for antibody-mediated rejection) were modest (mean [±SD] fluorescence intensity, 5660±2364), yet a high rate of rejection occurred (10 of 22 patients [45%] with donor-specific antibodies). These data raise serious concerns for higher-risk patients.

A high rate of delayed graft function (77% of patients) occurred in the U.S. cohort, despite a short cold ischemia time (mean, 19.9±5.2 hours). Did kidney biopsies that were performed in patients with delayed graft function reveal endothelial or renal tubular injury? Since donor-specific antibodies induce pathogenic signaling properties in endothelium,[2] it is important to determine whether $F(ab')_2$ donor-specific antibody fragments retain signaling properties, particularly if