and with our own experience, in which after a stepwise progression through other techniques of margin assessment, we adopted a policy of cavity shaving in 2008.[6] We would raise a few caveats. First, the rates of positive margins before randomization — 34% in the no-shave group and 36% in the shave group — seem high, and results similar to those obtained with cavity shaving have been reported for other methods. Second, the cosmetic effect of increasing the volume of resected tissue by 50% may not be apparent at the first postoperative visit, when seroma fills the excision cavity. Annual follow-up, as the authors plan, is critical to assess the final results of cavity shaving. Third, the presence and size of a DCIS component are significantly related to margin positivity, suggesting a role for predictive models: the added volume of resected tissue that is associated with cavity shaving may be worthwhile for some, but not all, patients. With or without cavity shaving, breast conservation always requires surgical judgment in order to find the proper balance between completeness of excision and acceptable cosmesis.

The ultimate goal of breast conservation is local control. Since the 10-year rates of local recurrence after breast-conserving surgery are already quite low (6% among patients with node-negative disease[7] and 9% among those with node-positive disease[8]), modifications in local treatment are unlikely to reduce them further. What can and should be reduced is the rate of reoperation, especially in an era that will increasingly link quality to value, rather than quantity, of care. A good starting point is consensus with regard to the margin definitions, and a new Society of Surgical Oncology–American Society for Radiation Oncology guideline defines no tumor on ink as adequate.[4] The challenge for breast imagers, surgeons, and pathologists will be to adopt additional evidence-based strategies that aim to maximize the rate of breast conservation, minimize reoperations, and maintain cosmesis. The current study is a strong step in the right direction.

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

From the Breast Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York.

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DOI: 10.1056/NEJMe1507190

Targeted Anti-Anticoagulants

Kenneth A. Bauer, M.D.

Four direct oral anticoagulants have been approved for use in many countries. These drugs are valuable alternatives to vitamin K antagonists, such as warfarin, for many patients requiring anticoagulation to prevent stroke due to nonvalvular atrial fibrillation and to treat and prevent venous thromboembolism. The mechanism of these agents is to selectively inhibit either thrombin or factor Xa, which are critical enzymes in the common pathway of blood coagulation. Dabigatran etexilate inhibits thrombin, whereas apixaban, edoxaban, and rivaroxaban inhibit factor Xa.

Direct oral anticoagulants have several pharmacologic advantages over vitamin K antagonists, including a wider therapeutic window, a rapid

onset of action, and shorter half-lives that range between 7 hours and 14 hours in healthy persons. Direct oral anticoagulants are administered at fixed doses to adults without laboratory monitoring, which is more convenient than warfarin with its requirement for monitoring of the international normalized ratio and periodic dose adjustments. In randomized trials with good anticoagulation management (i.e., with international normalized ratios generally in the desired therapeutic range of 2 to 3 for >60% of the time), direct oral anticoagulants were noninferior, and in some cases superior, to dose-adjusted warfarin for the prevention and treatment of thrombosis. As compared with warfarin, direct oral anticoagulants reduced the rate of major bleeding by 28% and the rates of intracranial and fatal hemorrhage by 50%.[1]

Despite the better bleeding profile of direct oral anticoagulants, as compared with warfarin, some physicians and patients have been unwilling to consider these drugs in the absence of an established way to reverse their anticoagulant activity. Although the anticoagulant activity of warfarin can be reversed with vitamin K, fresh-frozen plasma, and prothrombin complex concentrates, major bleeding events that occur in patients taking this drug often lead to poor outcomes; approximately 10% of patients who are hospitalized with warfarin-related bleeding die within 90 days,[2,3] and the mortality among patients with intracranial hemorrhage can be as high as 50%.[4,5] The high mortality is attributable in part to coexisting conditions in this patient population. Experimental data suggest that nonspecific reversal agents such as prothrombin complex concentrates, activated prothrombin complex concentrates, or recombinant factor VIIa can reduce the anticoagulant effect of direct oral anticoagulants in vitro, in animal models, and in human volunteers.[6] However, these agents are of unproven benefit in improving hemostasis in patients with bleeding related to direct oral anticoagulant use, and they carry a risk of thrombosis; thus, they are currently reserved for patients with severe bleeding who cannot be treated with supportive measures.

With the growing use of direct oral anticoagulants, it would be advantageous to have reversal agents that can rapidly and completely neutralize the anticoagulant activity of the drug and restore normal hemostasis. Specific reversal agents in clinical development include andexanet alfa, a recombinant factor Xa variant that specifically binds all the oral factor Xa inhibitors but lacks coagulant activity.[7] There is also a nonspecific reversal agent in clinical development, PER977, which binds to several of the direct oral anticoagulants by means of electrostatic interactions.[8] Given that there are no established reversal strategies for the direct oral anticoagulants, it is appropriate to undertake clinical trials of these agents without a control group.

Idarucizumab is a humanized monoclonal antibody fragment with high affinity for the oral direct thrombin inhibitor dabigatran that selectively and immediately neutralizes its anticoagulant activity.[9] Pollack et al.[10] now report in the *Journal* the results of an interim analysis of data from 90 patients who were taking dabigatran and who presented with either serious bleeding or the need for urgent surgery or intervention and received intravenous idarucizumab. This multicenter observational study evaluated the effect of a single 5-g dose of antibody in eligible patients who were judged by the treating clinician to require a reversal agent. The major end points of the study were pharmacodynamic assessments of the ability of idarucizumab to neutralize the anticoagulant activity of dabigatran. The data are convincing that the antidote effectively and immediately neutralized the activity of dabigatran with a satisfactory safety profile. Normal hemostasis was reported in more than 90% of the patients who underwent procedures after the administration of idarucizumab.

Without a control group, it is difficult to assess the clinical benefit that is conferred by the administration of idarucizumab in patients with dabigatran-related bleeding. The mortality in the study population was high at 20%; half the deaths occurred more than 96 hours after the administration of the antidote and were attributable to coexisting illness. Given that the half-life of dabigatran is 12 to 14 hours if renal function is normal, how important is it to be able to neutralize the anticoagulant activity of dabigatran rapidly in addition to providing supportive care measures? Major bleeding events in patients taking anticoagulants originate from anatomical lesions, and anticoagulation can lead to a rapid loss of blood from these sites. Thus, the location and size of the lesion along with the coexisting conditions of the patient may have a greater ef-

fect on prognosis than the ability to rapidly neutralize an anticoagulant that the patient is taking.

Laboratory measurements of the concentration of dabigatran were performed centrally in this study and were not used to guide therapy. The results of one of these tests, the dilute thrombin time, were normal on study entry in nearly one quarter of the study population. This group of patients had little or no circulating anticoagulant in their blood and would not be expected to benefit from the administration of idarucizumab. Thus, it will be useful to have activity measurements available for the various direct oral anticoagulants in real time to help guide the treatment of such patients and to prevent overutilization of what will surely be a costly medication.

The development of antidotes that are able to neutralize the activity of the various direct oral anticoagulants rapidly and completely is an important advance. When they become available, guidelines and clinical pathways will need to be developed to care effectively for patients with, or at risk for, major bleeding related to direct oral anticoagulant use. Additional studies, however, will be required to determine in which situations the antidotes improve clinical outcomes.

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

From Harvard Medical School and Beth Israel Deaconess Medical Center — both in Boston.

This article was published on June 22, 2015, at NEJM.org.

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DOI: 10.1056/NEJMe1506600