geography (distance from home to hospital), and even hospital administrative factors (prioritization of patients in a crowded ward). Possible varying practice among hospitals is unlikely to have influenced the main results, because we found no significant hospital–treatment interaction.

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Antithrombotic Therapy and Invasive Procedures

TO THE EDITOR: Baron et al. (May 30 issue)[1] make important suggestions in their review article; however, we propose that quantitative assessment of iatrogenic bleeding hazards must be considered as well as thrombosis prevention.[1] Although CHA_2DS_2–VASc scoring for atrial fibrillation is mentioned, the Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly (HAS-BLED) score for bleeding has also been validated.[2] Both scores calculate estimated annual risks and benefits and hence can guide future therapy.

Among the diverse causes of major bleeding outcomes associated with antithrombotic agents are periprocedural, intracranial, and gastrointestinal causes.[3] Although few therapies can treat and prevent the first two factors, data from a large, randomized trial show that proton-pump inhibitors are safe for concomitant use with antithrombotic agents.[4] Given the shorter time frame in which medications are being withheld for procedures, the absolute thrombotic or bleeding risks can be overstated; however, bleeding (and its consequences) remains an important iatrogenic issue. Populations globally are also being treated increasingly with combinations of antithrombotic therapies and medications such as nonsteroidal antiinflammatory drugs (NSAIDs), which can intensify such bleeding risks.[5] Hence, further quantitative research, including validation of cause-specific bleeding scores associated with antithrombotic agents, is paramount to guide clinical management.

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No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: The review article by Baron et al. does not address the clinical safety and efficacy of new antithrombotic agents in patients with cancer who are undergoing surgical procedures. A sizable number of patients with cancer undergo surgery or procedures with local or regional anesthesia. Trials of oral direct thrombin inhibitors and oral factor Xa inhibitors have enrolled less than 5% of patients with cancer.[1] Because of a lack of data, the American Society of Clinical Oncology recommends against the use of new oral anticoagulants (for prevention and treatment) in patients with cancer.[2] These patients also frequently require anesthesia to undergo long invasive procedures. The American Society of Regional Anesthesia and Pain Medicine recommends cautious use of these agents in patients undergoing neuraxial anesthesia.[3] The lack of both efficacy data and an antidote for reversibility of bleeding should prompt clinicians to be cautious while administering the new anticoagulants in

patients with cancer who are likely to undergo invasive procedures.

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TO THE EDITOR: The panel on the 2012 guidelines of the American College of Chest Physicians (ACCP) on periprocedural antithrombotic therapy concluded that the quality of evidence for bridging therapy, even in patients with "high" thrombotic risk, was weak enough to warrant only grade 2C recommendations.[1] This is the weakest recommendation possible and supports the suggested (not required) use of bridging therapy in any patient group. Two ongoing placebo-controlled trials (not one, as stated by Baron and colleagues) are investigating bridging therapy. These trials are Bridging Anticoagulation in Patients Who Require Temporary Interruption of Warfarin Therapy for an Elective Invasive Procedure or Surgery (ClinicalTrials.gov number, NCT00786474) and A Double Blind Randomized Control Trial of Post-Operative Low Molecular Weight Heparin Bridging Therapy Versus Placebo Bridging Therapy for Patients Who Are at High Risk for Arterial Thromboembolism (NCT00432796).

With respect to restarting therapy, most guidelines recommend restarting anticoagulation within 24 hours after a procedure involving a low risk of bleeding. Waiting 48 hours, as Baron et al. suggest, may expose a patient to the risk of thromboembolism. For procedures involving a high risk of bleeding, waiting 48 to 72 hours or considering a stepwise increase in antithrombotic therapy is suggested.[2]

Table 4 of the article by Baron et al. incorrectly recommends the use of anti–factor Xa "antibody" levels to monitor treatment with low-molecular-weight heparin, rivaroxaban, and apixaban. Table 2 includes content from Table 1 in the 2012 ACCP guidelines on periprocedural antithrombotic agents and should cite this reference.[1]

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TO THE EDITOR: Baron et al. offer some very practical advice for treating patients who are receiving warfarin and who require bridging anticoagulation therapy for procedures. Unfortunately, some of their advice could lead to undesirable outcomes. Patients with deficiencies in protein C, S, or both or dysproteinemia of either protein C or S require full therapeutic anticoagulation with heparin (or a low-molecular-weight heparin) before initiation of warfarin; otherwise, they are at risk for the development of the prothrombotic state described as warfarin-induced skin necrosis.[1,2] It is important to be aware of this when recommending the postoperative timing of initiation of heparin (or a low-molecular-weight heparin) and warfarin.

Although typically it takes 5 to 7 days of warfarin therapy to achieve anticoagulation, the half-life of prothrombin is approximately 72 hours, and patients with an international normalized ratio (INR) of more than 1.9 do not receive anticoagulation therapy immediately. To avoid a period of inadequate anticoagulation, the bridging heparin should not be discontinued when the INR is at a therapeutic level, but rather it should be continued at least 24 and preferably 48 hours after the INR is more than 1.9.

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TO THE EDITOR: The article by Baron et al. contains some inconsistencies. The authors propose continuation of antithrombotic agents in patients undergoing cataract surgery and receiving intraocular injections, since these procedures are considered to be associated with a low risk of bleeding (<1.5%). Periorbital and vitreoretinal surgeries are classified as procedures associated with a high risk of bleeding (>1.5%) and, therefore, in patients who are at low risk for thrombotic events, anticoagulation therapy may be temporarily discontinued without the use of bridging therapy, whereas for selected high-risk patients, bridging therapy is strongly recommended (Table S1 in the Supplementary Appendix of the article, available at NEJM.org). However, this statement contradicts their proposal that procedures that can result in intraocular bleeding are associated with high risk and classified as major. Likewise, prospective cohort studies in cataract surgery have shown an incidence of clinically important bleeding of up to 3%.[1] Peribulbar anesthesia[2] and transconjunctival sutureless vitrectomies[3] may be safe in these patients. Finally, one editorial has suggested that the risk of a cardiovascular event among patients in whom anticoagulant and antiplatelet agents are discontinued is higher than the risk of bleeding during ocular surgery among patients who continue to receive these drugs.[4]

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THE AUTHORS REPLY: In reply to the comments by Verma and Bhala: better predictors of bleeding are needed in patients receiving antithrombotic agents and NSAIDs, and data to support management recommendations are lacking. The comment regarding proton-pump inhibitors relates to spontaneous bleeding, which was not our focus.

With regard to the comments by Yusuf and Zalpour: we appreciate the citation to the American Society of Clinical Oncology recommendations and agree that treatment with a periprocedural antithrombotic agent is also important in patients undergoing neuraxial anesthesia.[1]

With regard to the comments by Spyropoulos and Ortel: the risk of periprocedural bleeding is triple that of the risk of thromboembolism; full-dose parenteral anticoagulants administered for 24 hours or less increase bleeding risk.[2] Therefore, we withhold full-dose parenteral anticoagulants for 48 hours unless the risk of bleeding is low. Anti–factor Xa assays can be used for monitoring of anticoagulant effects.[3] We apologize for not citing the ACCP guidelines (reference 2 of our article) in Table 2.

Bomzer describes the risk of warfarin-induced skin necrosis due to deficiencies in protein C, S, or both or dysproteinemia; however, this condition is rare. In the general population, the prevalence of this condition due to deficiency in protein C is 1 case per 200 to 500 persons, and the prevalence of this condition due to deficiency in protein S is 1 case per 800 persons. Heparin bridging during warfarin initiation appears to be warranted in these patients. However, universal bridging therapy for atrial fibrillation alone (estimated U.S. prevalence, 2.7 million to 6.1 million cases) would greatly increase adverse events such as heparin-induced thrombocytopenia. New

anticoagulants may prevent warfarin-induced skin necrosis but cannot be recommended yet.

Finally, in reply to Grzybowski and Ascaso: the use of antithrombotic agents in ocular surgery remains highly controversial. The stated bleeding rate of 3% is excessive in modern cataract surgery. This avascular procedure, which is frequently performed with topical anesthesia, avoids potential retrobulbar hemorrhage due to retrobulbar anesthesia. However, retrobulbar anesthesia is frequently used in vitreoretinal surgery. Catastrophic bleeding during vitreoretinal surgery can be due to choroidal hemorrhage and neovascularization in proliferative retinal diseases. Bleeding after sutureless vitreoretinal surgery may be uncontrolled, since hypotonia in an open eye prevents tamponade.

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Case Reports of PML in Patients Treated for Psoriasis

TO THE EDITOR: In their letters about patients who were receiving oral dimethyl fumarate for the treatment of psoriasis, Ermis et al.[1] and van Oosten et al.[2] (April 25 issue) state that progressive multifocal leukoencephalopathy (PML) had been diagnosed in two patients. Dimethyl fumarate is the active ingredient in Fumaderm, which since 1994 has been registered for the treatment of psoriasis in Germany. Leukopenia and lymphopenia are known adverse effects of such therapy.

The summary of product characteristics for Fumaderm and current guidelines recommend that in all patients receiving the drug, a differential blood count should be obtained every 2 to 3 months and the drug should be terminated if the leukocyte count is below 3000 per cubic millimeter or the lymphocyte count is below 500 per cubic millimeter.[3,4] In the safety database of the German drug agency (BfArM), which covers more than 180,000 patient-years of Fumaderm exposure, no cases of PML have been documented in patients in whom these rules were applied. In contrast, in all cases of PML observed in association with therapy with dimethyl fumarate, physicians have not adequately treated lymphopenia. The two patients who are described in the *Journal* both had lymphocyte counts below the threshold of 500 per cubic millimeter for more than 2 years. It appears, therefore, that these cases of PML occurred after long-standing, severe lymphopenia, which has been identified as a primary risk factor for PML.[5]

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