and Drug Administration–approved antihelminthic drug, as a novel Wnt–β-catenin inhibitor. By administering pyrvinium to Apc-haploinsufficient mice, they were able to rescue the anemia and prolong survival, again correlating this in vivo mechanism with inhibition of β-catenin activation within MSCs. Finally, they validated the efficacy of pyrvinium to inhibit β-catenin activation in primary, patient-derived del(5q) MDS samples (see figure). In the current study, pyrvinium was able to prevent, or delay, the development of anemia, but was less effective in ameliorating established anemia. This suggests that early identification and treatment of susceptible patients is essential to the success of this approach.

Like many excellent studies, this work raises a number of ongoing questions. First, how frequently is β-catenin activated within the MDS niche, and is this activation linked to the MDS cytogenetic or molecular genotype? Does aberrant β-catenin signaling contribute to clonal development and AML progression from MDS, and is it required for maintenance of LSCs? Which are the pathologic cell populations within the MDS niche and what is the best compound to therapeutically target β-catenin activation in vivo? Finally, how do we identify at-risk MDS patients early enough in their disease that they are likely to benefit from this approach?

Clinical hematologists is in the midst of a genomics revolution, with the increasingly widespread availability of next-generation sequencing for blood cancers. For practicing clinicians, the application of these data are often challenging, and approaches that focus on common, deregulated pathways offer practical and pragmatic solutions. With the current study, Stoddart and colleagues provide a novel approach to manipulate the stem cell niche, an avenue that is likely to have broad implications and may help treat patients with MDS and related malignancies.

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CLINICAL TRIALS AND OBSERVATIONS

Comment on Lopes et al, page 2980

A glimmer of hope for a devastating complication

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In this issue of Blood, Lopes et al report that patients with atrial fibrillation suffered from intracerebral and subdural hemorrhage less frequently when they were treated with apixaban than with warfarin, despite the warfarin anticoagulation being within therapeutic ranges in the majority of cases.1

Intracranial hemorrhage (ICH) during anticoagulation therapy is a devastating complication. Approximately 75% of anticoagulated patients with spontaneous intracerebral hemorrhage die or remain severely disabled 1 year after the stroke.2 For decades, vitamin K antagonists (VKAs) such as warfarin have been the mainstay of anticoagulation therapy for the prevention of thromboembolic events in patients with atrial fibrillation. The introduction of direct oral anticoagulants (DOACs), at that time also referred to as “novel” oral anticoagulants, was well received because they are effective in overcoming several shortcomings of VKA. However, without antidotes, major concerns were raised that bleeding complications such as ICH could have disastrous consequences for patients (see figure). These concerns were intensively debated within the medical community,3 but they also gained attention in the press. Pharmaceutical companies were sued on this issue. Today, experience with these agents has increased considerably and registry analyses have confirmed advantages in specific patient populations in pivotal clinical trials.4 Limited data are available regarding the characteristics of ICH during DOAC treatment, but several studies have shown that mortality and neurological outcome seem comparable to that of patients with ICH during VKA treatment.

The present study clearly demonstrates that treatment with the factor Xa inhibitor apixaban is associated with a significantly lower rate of ICH than treatment with warfarin (0.33%/year vs 0.80%/year). These findings are in concordance with the results of other studies on DOAC such as dabigatran, edoxaban, and rivaroxaban.6 Importantly, the authors demonstrate that the risk for ICH is not only decreased for the occurrence of spontaneous ICH, but also for traumatic ICH. Moreover, hematomas occurred less frequently in intracerebral locations and in the subdural compartment. This finding is important because these 2 types of ICH have very different etiologies and pathophysiological mechanisms. Spontaneous intracerebral hematomas are located within brain tissue, leading to immediate primary neuronal damage and secondary neuronal damage resulting from inflammatory and ischemic processes. They most commonly occur in patients with...
underlying cerebrovascular disease, often as a result of risk factors such as arterial hypertension. The prognosis of spontaneous intracerebral hemorrhage is considered poor, even in the absence of anticoagulation therapy. Subdural hematomas are located on the brain’s surface, and neuronal damage is caused when a hematoma reaches a size that exerts pressure on brain tissue. Anticoagulated patients who suffer from subdural hemorrhage (eg, after mild head trauma) are at particular risk for neurological deterioration resulting from hematoma enlargement from impaired hemostasis. The presence of a subdural hematoma is a potentially life-threatening condition, but a favorable outcome can be achieved if excessive pressure on brain tissue can be avoided. Thus, surgical evacuation of a subdural hematoma represents an effective method to reduce space-occupying effects on brain tissue for symptomatic subdural hematomas.\textsuperscript{7} In contrast, the role of surgery in the treatment of intracerebral hemorrhage has not yet been well defined, and several attempts to improve patient outcomes have failed in clinical trials.\textsuperscript{9}

The present findings should be taken into account when considering anticoagulation therapy with apixaban for atrial fibrillation: it should not be withheld from patients because of the unavailability of a specific antidote. The study by Lopes et al also demonstrates that comedication with aspirin significantly increased the risk of ICH. Notably, only half of the ICH patients had a formal indication for aspirin therapy; therefore, the risk–benefit ratio has to be carefully evaluated when deciding on antiplatelet treatment.

It is quite striking that attempts to reverse anticoagulation were made in only a minority of ICH patients in the present study. For instance, vitamin K was administered in just 16 of 122 patients with ICH on warfarin treatment. This practice does not reflect the recommendations of current guidelines.\textsuperscript{8,9} Further research into anticoagulation reversal strategies is mandatory for improving treatment of patients with ICH. The potential and limitations of specific antidotes are under investigation and, recently, a specific antidote to reverse the effects of factor Xa inhibitors has shown encouraging results in restoring hemostasis in patients with bleeding complications.\textsuperscript{10} Given their safety profile, DOAC would be further enhanced by optimizing treatment protocols for the management of patients who do develop ICH.

Despite several advantages of DOAC in the treatment of patients with atrial fibrillation, a fact has to be kept in mind: ICH during anticoagulation therapy remains a devastating condition and this applies to both types of anticoagulation, VKA and DOAC. Considering the social burden of this disease, especially in the elderly population of industrialized countries, this issue has to be addressed urgently in future studies.

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A glimmer of hope for a devastating complication

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