Patients with cancer commonly have a venous thromboembolism during the course of their disease. Venous thromboembolism in these patients leads to a high risk of recurrence and bleeding related to anticoagulant therapy. Furthermore, venous thromboembolism exposes patients with cancer to the risk of interruption of cancer treatment and may lead to otherwise unnecessary hospitalization. For these reasons, prevention of venous thromboembolism in ambulatory patients with cancer who are receiving chemotherapy is of potential clinical value.

In two large, randomized, placebo-controlled trials and a comprehensive meta-analysis, all involving ambulatory patients with different types of metastatic or locally advanced solid cancer who were receiving chemotherapy, low-molecular-weight heparins were associated with an approximately 50% lower risk of symptomatic venous thromboembolism than placebo. The incidence of symptomatic venous thromboembolism in the placebo group and the absolute difference in risk between the trial groups were considered too low to recommend antithrombotic prophylaxis. Several international guidelines suggest that antithrombotic prophylaxis be considered only in high-risk patients.

This consideration led to the concept that stratification for the risk of venous thromboembolism and the consequent use of prophylaxis only in high-risk patients could improve the clinical benefit by reducing the number needed to treat to avoid an episode of venous thromboembolism. Several strategies have been proposed to identify patients with cancer who have a high risk of venous thromboembolism. These strategies include specific cancer type or chemotherapy regimen or predictive scores based on a combination of clinical and laboratory risk factors, including the Khorana score, a risk-assessment algorithm that uses the type of cancer, pretreatment hematologic factors (hemoglobin level, white-cell count, and platelet count), and body-mass index to quantify risk.

This issue of the Journal includes two trials of direct oral anticoagulants for the prevention of venous thromboembolism in high-risk ambulatory patients with cancer, with risk defined by the Khorana score. In the Apixaban for the Prevention of Venous Thromboembolism in High-Risk Ambulatory Cancer Patients (AVERT) trial, apixaban was associated with a significantly lower incidence of venous thromboembolism than placebo in the primary intention-to-treat population but also with a higher incidence of major bleeding episodes. In the CASSINI trial, the incidence of venous thromboembolism was lower with rivaroxaban than with placebo in the per-protocol analysis but not in the primary intention-to-treat analysis; no significant between-group difference in major bleeding was observed.

When considered together, the two trials showed a significant benefit of direct oral anticoagulants for the prevention of venous thromboembolism, with a low incidence of major bleeding (Table 1). The findings related to bleeding are quite reassuring, given the increase in bleeding observed with apixaban and rivaroxaban in studies on the prophylaxis of venous thromboembolism involving medical patients without cancer. In the current trials combined, there was not a significant difference in mortality between patients who received a direct oral anticoagulant and those who received placebo.

Will these trials change clinical practice? Although the evidence provided by the two trials is
Mechanisms of platelet activation and aggregation in health and disease.

The role of platelets in hemostasis and thrombosis is well-established. Platelets are formed by the fragmentation of megakaryocytes in the bone marrow and are essential for hemostasis and vessel repair. Platelets are activated in response to a variety of stimuli, including shear stress, tissue injury, and the release of inflammatory mediators. Activation of platelets leads to the release of granule contents, including adenosine diphosphate (ADP), thromboxane A2 (TXA2), and serotonin, which promote further platelet aggregation and thrombus formation. 

Platelets also play a crucial role in the immune system, participating in the regulation of inflammation and the clearance of pathogens. Platelets are involved in the recognition and phagocytosis of pathogenic microorganisms and in the activation of the complement system. Platelets also contribute to the formation of immune complexes and the regulation of cytokine production.

In recent years, there has been growing interest in the role of platelets in the pathogenesis of various diseases, including cardiovascular disease, cancer, and autoimmune disorders. The activation of platelets is associated with the development of atherosclerosis, the formation of thrombi, and the progression of cardiovascular disease. Platelet activation also plays a role in the metastasis of cancer cells and the development of thrombotic complications in patients with cancer.

Platelets are also involved in the pathogenesis of autoimmune disorders, including systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). In SLE, platelet activation is associated with the release of inflammatory mediators and the activation of the complement system, leading to the formation of immune complexes and the deposition of immune complexes in various tissues. In RA, platelet activation is involved in the development of joint inflammation and the recruitment of inflammatory cells.

In summary, platelets are essential for hemostasis and vessel repair, and their activation plays a crucial role in the pathogenesis of various diseases. Understanding the mechanisms of platelet activation and aggregation is essential for the development of new therapeutic strategies for the prevention and treatment of these diseases.
benefit associated with prophylaxis with direct oral anticoagulants in ambulatory patients with cancer.

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Needed: Antimicrobial Development

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Antimicrobial resistance continues to erode our therapeutic armamentarium for treating patients with bacterial infections. Clinicians are now encountering infections that are susceptible to few or even (although rarely) none of the available drugs. One of the multiple components of a strategy to effectively respond to antimicrobial resistance — the development of new antibacterial agents — is particularly challenging because of the nature of serious acute bacterial infections and the economic realities in this field. The initiation of antimicrobial therapy is urgently needed in patients with serious acute bacterial infections. Initiation is often recommended within an hour after presentation, despite the diagnostic uncertainty during the first few days of treatment, especially regarding the identification of the infecting pathogen and its antimicrobial susceptibility. In a clinical trial, initial empirical treatment before enrollment or concomitant antibacterial therapy may be necessary for effective management of the infection, but either one of these may also interfere with the interpretation of the effect of the test drug that is being studied in a trial.

The induction, amplification, and dissemination of elements of antimicrobial resistance among microbes make appropriate stewardship of a new antibacterial agent essential both for the patient and for the community. In addition, most antibacterial treatment courses are short (often a week or two), and antimicrobial stewardship seeks to limit the use of broader spectrum agents, whenever appropriate, to preserve their usefulness, thereby minimizing the use of newer agents. In contrast, in many other therapeutic areas such as diabetes, hypertension, and hyperlipidemia, daily use by patients over a period of years does not contribute to the loss of efficacy of the agent, and there is no medical reason to delay use. Although antimicrobial stewardship is absolutely essential, from the point of view of a drug developer it will most likely reduce the economic returns. Reports of financial stress related to industry development of antibacterial drugs are not new.

In this issue of the Journal, Wagenlehner et al. and McKinnell et al. report the results of two clinical trials designed to evaluate plazomicin, an aminoglycoside that was developed to target