EDITORIALS

Direct Oral Anticoagulants for Thromboprophylaxis in Ambulatory Patients with Cancer

Giancarlo Agnelli, M.D.

Patients with cancer commonly have a venous thromboembolism during the course of their disease.[1] Venous thromboembolism in these patients leads to a high risk of recurrence and bleeding related to anticoagulant therapy.[2] 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[3,4] and a comprehensive meta-analysis,[5] 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.[6]

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.[7]

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,[8] 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,[9] 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

The New England Journal of Medicine
Downloaded from nejm.org by The NEJM iPad Edition on April 10, 2019. For personal use only. No other uses without permission.
Copyright © 2019 Massachusetts Medical Society. All rights reserved.

Table 1. Cumulative Analysis of the AVERT and CASSINI Trials.*

Outcome	CASSINI Trial		AVERT Trial		Cumulative Values				
	Rivaroxaban	Placebo	Apixaban	Placebo	DOACs	Placebo	Relative Risk (95% CI)	Absolute Difference	No. Needed to Treat or Harm†
	number/total number (percent)							*percentage points*	
Primary efficacy outcome									
ITT analysis	25/420 (6.0)	37/421 (8.8)	12/288 (4.2)	28/275 (10.2)	37/708 (5.2)	65/696 (9.3)	0.56 (0.38–0.83)	−4.1	24
Analysis during treatment period	11/420 (2.6)	27/421 (6.4)	3/288 (1.0)	20/275 (7.3)	14/708 (2.0)	47/696 (6.8)	0.29 (0.16–0.53)	−4.8	21
Symptomatic VTE: ITT analysis	15/420 (3.6)	19/421 (4.5)	9/288 (3.1)	22/275 (8.0)	24/708 (3.4)	41/696 (5.9)	0.58 (0.35–0.94)	−2.5	40
Major bleeding	8/405 (2.0)	4/404 (1.0)	10/288 (3.5)	5/275 (1.8)	18/693 (2.6)	9/679 (1.3)	1.96 (0.88–4.33)	1.3	77
Death from any cause	84/420 (20.0)	100/421 (23.8)	35/288 (12.2)	27/275 (9.8)	119/708 (16.8)	127/696 (18.2)	0.92 (0.73–1.16)	−1.4	71

* In the AVERT trial, the modified intention-to-treat analysis was the primary analysis (574 patients underwent randomization). DOACs denotes direct oral anticoagulants, ITT intention to treat, and VTE venous thromboembolism.
† The number needed to treat is shown for all outcomes except major bleeding (number needed to harm).

quite compelling, some clinicians could still be reluctant to change their practice. Indeed, some of the most common cancers, such as colorectal, breast, and prostate cancers, were underrepresented in the two trials. The Khorana score, the cornerstone of the two trials, has been shown to perform poorly in some cancer types, such as lung cancer,[10] which accounts for 13% of all cancers and 24% of cancer deaths in the United States. Furthermore, this score does not take into account the chemotherapy regimen. All these considerations may limit the generalizability of the AVERT and CASSINI trials, and some clinicians may consider that data on individual cancer types or individual chemotherapy agents are required before prophylaxis can be generally accepted.

If the reason for using the Khorana score was to reduce the number needed to treat, the results appear to be relatively modest. Indeed, when the results of the two studies are combined, the absolute difference in the incidence of symptomatic venous thromboembolism between the active-drug group and the placebo group in the primary intention-to-treat analysis was 2.5 percentage points, which corresponds to a number needed to treat of 40 patients (Table 1). This number is only marginally more favorable than those achieved in studies that did not use any risk score as an entry criterion and that had symptomatic events as the primary study outcome, and it is higher than those seen in the subgroups of patients with lung, colon, and pancreatic cancer or receiving chemotherapy with platinum compounds.[3-5]

In the current trials, the percentage of patients who continued the trial regimen for the entire treatment period was relatively low and could not be explained by the expected deaths in a population that included many patients with advanced cancer. This finding confirms the complexity of treating patients with cancer, regardless of the route of administration.

In conclusion, the AVERT and CASSINI trials showed that thromboprophylaxis with direct oral anticoagulants in ambulatory patients with cancer was effective and safe. The patients had different types of cancer and were considered to be at high risk for venous thromboembolism according to the Khorana score. Trials involving patients with individual types of cancer would provide the definitive evidence about the clinical

The New England Journal of Medicine
Downloaded from nejm.org by The NEJM iPad Edition on April 10, 2019. For personal use only. No other uses without permission.
Copyright © 2019 Massachusetts Medical Society. All rights reserved.

benefit associated with prophylaxis with direct oral anticoagulants in ambulatory patients with cancer.

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

From the Internal Vascular and Emergency Medicine–Stroke Unit, University of Perugia, Perugia, Italy.

1. Lyman GH, Eckert L, Wang Y, Wang H, Cohen A. Venous thromboembolism risk in patients with cancer receiving chemotherapy: a real-world analysis. Oncologist 2013;18:1321-9.
2. Prandoni P, Lensing AW, Piccioli A, et al. Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. Blood 2002;100:3484-8.
3. Agnelli G, Gussoni G, Bianchini C, et al. Nadroparin for the prevention of thromboembolic events in ambulatory patients with metastatic or locally advanced solid cancer receiving chemotherapy: a randomised, placebo-controlled, double-blind study. Lancet Oncol 2009;10:943-9.
4. Agnelli G, George DJ, Kakkar AK, et al. Semuloparin for thromboprophylaxis in patients receiving chemotherapy for cancer. N Engl J Med 2012;366:601-9.
5. Di Nisio M, Porreca E, Candeloro M, De Tursi M, Russi I, Rutjes AW. Primary prophylaxis for venous thromboembolism in ambulatory cancer patients receiving chemotherapy. Cochrane Database Syst Rev 2016;12:CD008500.
6. Lyman GH, Bohlke K, Khorana AA, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology clinical practice guideline update 2014. J Clin Oncol 2015;33:654-6.
7. Khorana AA, Kuderer NM, Culakova E, Lyman GH, Francis CW. Development and validation of a predictive model for chemotherapy-associated thrombosis. Blood 2008;111:4902-7.
8. Carrier M, Abou-Nassar K, Mallick R, et al. Apixaban to prevent venous thromboembolism in patients with cancer. N Engl J Med 2019;380:711-9.
9. Khorana AA, Soff GA, Kakkar AK, et al. Rivaroxaban for thromboprophylaxis in high-risk ambulatory patients with cancer. N Engl J Med 2019;380:720-8.
10. Kuderer NM, Poniewierski MS, Culakova E, et al. Predictors of venous thromboembolism and early mortality in lung cancer: results from a global prospective study (CANTARISK). Oncologist 2018;23:247-55.

DOI: 10.1056/NEJMe1816060
Copyright © 2019 Massachusetts Medical Society.

Needed: Antimicrobial Development

Edward Cox, M.D., M.P.H., Sumathi Nambiar, M.D., M.P.H., and Lindsey Baden, M.D.

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,[1] 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.[2]

In this issue of the *Journal*, Wagenlehner et al.[3] and McKinnell et al.[4] report the results of two clinical trials designed to evaluate plazomicin, an aminoglycoside that was developed to target

The New England Journal of Medicine
Downloaded from nejm.org by The NEJM iPad Edition on April 10, 2019. For personal use only. No other uses without permission.
Copyright © 2019 Massachusetts Medical Society. All rights reserved.