Response

To the Editor:

We thank Drs Chang and Hancox for their interest in our work on natriuretic peptides in community-acquired pneumonia.1,2 The current report1 extends our previous observations and tries to highlight findings that (1) apply to the whole family of natriuretic peptides in general and (2) provide a direct comparison of the clinical potential of all three commercially available natriuretic peptides (B-type natriuretic peptide [BNP], N-terminal pro-B-type natriuretic peptide, and midregional pro-atrial natriuretic peptide). In this analysis, we used the data from all patients who presented to our institution with community-acquired pneumonia in whom we had the measurements of all three natriuretic peptides available. As correctly mentioned by Drs Chang and Hancox, some of these patients were in earlier cohorts that dealt exclusively with BNP. About one-third of the patients were included in the recruitment period from April 2006 to March 2007.

Drs Chang and Hancox are also correct in highlighting that in some patients, physicians used procalcitonin levels as additional information for the tailoring of the duration of antibiotic treatment. Regarding blinding, physicians were blinded to N-terminal pro-B-type natriuretic peptide and midregional pro-atrial natriuretic peptide levels in all patients. These levels were measured from frozen samples long after the discharge of patients. The blinding regarding BNP levels was not uniform. In about one-half of the patients, BNP levels were measured in a blinded fashion; in the other half, BNP levels would have been available to physicians via the electronic patient records.

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Preventing VTE in Outpatients With Cancer

To the Editor:

We applaud the innovations pioneered by the American College of Chest Physicians evidence-based clinical practice guidelines on antithrombotic therapy and prevention of thrombosis (February 2012). However, we are concerned about the resulting recommendations regarding cancer-associated thrombosis, a significant contributor to the public health burden of VTE and an area of particular interest to us.

Regarding prevention of VTE in nonsurgical patients,1 the panel suggested that outpatients with solid tumors with additional risk factors for VTE should receive prophylactic-dose low-molecular-weight heparin or low-dose unfractionated heparin (recommendation 4.2.2). Additional risk factors cited by the panel include hormonal therapy and angiogenesis inhibitors. In our opinion, this recommendation (even as a grade 2B) does not reflect an appropriate interpretation of the results of recent studies on cancer thromboprophylaxis and risk assessment. If these recommendations were to be followed, tens of thousands of women with breast cancer or men with prostate cancer on hormonal therapy for extended periods would receive low-molecular-weight heparin or low-dose unfractionated heparin. The rate of VTE in these patients, however, is much lower than other cancer subgroups, and there are no studies showing a benefit of thromboprophylaxis.2 Similarly, the link between antiangiogenic agents, such as bevacizumab, and VTE has not been consistently demonstrated in pooled analyses.2 (Although thalidomide- and lenalidomide-based regimens are associated with VTE, these are used primarily in myeloma and not solid tumors.) Recommendation 4.2.2 further fails to cite important risk factors, such as site of cancer, and a risk assessment model for chemotherapy-associated VTE that has been externally validated in multiple studies; both are the basis for recent and ongoing prophylaxis studies.2

The Institute of Medicine’s 2011 report, Clinical Practice Guidelines We Can Trust, emphasized guideline development group composition and external review.3 Inclusion of oncology content experts on the panel or as external reviewers could have provided a different interpretation of the data and more

References


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The Institute of Medicine’s 2011 report, Clinical Practice Guidelines We Can Trust, emphasized guideline development group composition and external review.3 Inclusion of oncology content experts on the panel or as external reviewers could have provided a different interpretation of the data and more
clinically sound recommendations. We urge the panel to consider such multidisciplinary input for the next iteration of the guidelines. Even weak recommendations formulated without scientific evidence can have a negative impact on patient care and future study design. It is quite possible that institutional review boards may identify these suggestions as the standard of care, affecting future study feasibility. As physicians and researchers involved in this field, we disagree with recommendation 4.2.2 and suggest that clinicians consider recommendations from cancer-focused guidelines, such as those of the American Society of Clinical Oncology and the National Comprehensive Cancer Network.

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REFERENCES


Response

To the Editor:

We thank Dr Khorana and his colleagues for their thoughtful comments on our article. 1 As a point of clarification, our recommendation does not suggest that patients “should receive” prophylactic-dose heparin. In fact, it is a weak (level 2) recommendation, only suggesting the use of a prophylactic dose of heparin and only in subgroups of patients with cancer at high risk of VTE and low risk of bleeding. Indeed, within the Gradation of Recommendation, Assessment, Development, and Evaluation framework, panel members make a weak recommendation when they conclude that the desirable effects of adherence to the recommendation probably outweigh the undesirable effects. 2 In those cases, the best action may differ depending on patient circumstances, 3 and clinicians need to help each patient make a decision consistent with her or his values and preferences. 2

The authors suggest that the recommendation is formulated without scientific evidence. The scientific evidence the panel considered is summarized in Table 15 of the article and in Table S18 of the online supplement. 1 It is based on a Cochrane systematic review, 4 with a meta-analysis of nine trials at low risk of bias, enrolling 2,857 patients. The quality of evidence was rated high for symptomatic VTE; moderate for mortality, major bleeding, and minor bleeding; and low for quality of life. The recent publication of two trials 5,6 has further increased the quality of evidence and the precision of effect estimates. 7

The guideline panel carefully considered the balance of benefits and harms for this recommendation. According to the data in Table 15, 1 if 1,000 patients with cancer were to use a prophylactic dose of heparin, over a follow-up period of 12 months death would likely be averted in approximately 45 patients, symptomatic VTE would be averted in 13, and two would have a major bleeding episode. Considering this trade-off, along with the burden of a daily injection of heparin over a prolonged period of time, the panel made the judgment that patients are more likely to benefit than be harmed and issued a weak recommendation in favor.

The guideline panel was also very concerned with the issue raised by the authors (ie, the identification of patients who are more likely to benefit from heparin prophylaxis). Indeed, as we point out in the article, “the substantial clinical heterogeneity of the patients studied (different cancer types, different cancer treatments, and different durations of prophylaxis) raises questions about which groups of outpatients with cancer will benefit.” 1 8 Therefore, the panel issued a first recommendation (recommendation 4.2.1) that advises against routine prophylaxis with heparin in outpatients with cancer who have no additional risk factors for VTE. It then issued a second recommendation (recommendation 4.2.2) suggesting prophylactic-dose heparin in a well-defined