REFERENCES

1. Nowak A, Breidhardt T, Christ-Crain M, et al. Direct comparison of three natriuretic peptides for prediction of short- and long-term mortality in patients with community-acquired pneumonia. *Chest*. 2012;141(4):974-982.
2. Christ-Crain M, Breidhardt T, Stolz D, et al. Use of B-type natriuretic peptide in the risk stratification of community-acquired pneumonia. *J Intern Med*. 2008;264(2):166-176.
3. Müller C, Laule-Kilian K, Scholer A, Perruchoud AP. B-type natriuretic peptide for risk stratification in community-acquired pneumonia. *J Intern Med*. 2005;258(4):391-393.
4. Christ-Crain M, Stolz D, Bingisser R, et al. Procalcitonin guidance of antibiotic therapy in community-acquired pneumonia: a randomized trial. *Am J Respir Crit Care Med*. 2006;174(1):84-93.

Response

To the Editor:

We thank Drs Chang and Hancox for their interest in our work on natriuretic peptides in community-acquired pneumonia.¹⁻⁴ 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.

Christian Müller, MD
Basel, Switzerland
Albina Nowak, MD
Zurich, Switzerland

Affiliations: From the Department of Internal Medicine (Dr Müller), University Hospital Basel; and the University Hospital Zurich (Dr Nowak).

Financial/nonfinancial disclosures: The authors have reported to *CHEST* the following conflicts of interest: Dr Müller has received research support and speakers' honoraria from Abbott Laboratories, Alere, BRAHMS, Nanosphere Inc, Hoffman-La Roche Inc, and Siemens AG. Dr Nowak has reported that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

Correspondence to: Christian Müller, MD, University Hospital Basel, Department of Internal Medicine, Petersgraben 4, Basel, 4031, Switzerland; e-mail: chmueller@uhbs.ch

© 2012 American College of Chest Physicians. Reproduction of this article is prohibited without written permission from the American College of Chest Physicians. See online for more details. DOI: 10.1378/chest.12-0516

REFERENCES

1. Novak A, Breidhardt T, Christ-Crain M, et al. Direct comparison of three natriuretic peptides for prediction of short- and long-term mortality in patients with community acquired pneumonia. *Chest*. 2012;141(4):974-982.
2. Christ-Crain M, Breidhardt T, Stolz D, et al. Use of B-type natriuretic peptide in the risk stratification of community-acquired pneumonia. *J Intern Med*. 2008;264(2):166-176.
3. Müller C, Laule-Kilian K, Scholer A, Perruchoud AP. B-type natriuretic peptide for risk stratification in community-acquired pneumonia. *J Intern Med*. 2005;258(4):391-393.
4. Christ-Crain M, Stolz D, Bingisser R, et al. Procalcitonin guidance of antibiotic therapy in community-acquired pneumonia: a randomized trial. *Am J Respir Crit Care Med*. 2006;174(1):84-93.

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 linkage between antiangiogenic agents, such as bevacizumab, and VTE has not been consistently demonstrated in pooled analyses.³ (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.⁴

The Institute of Medicine's 2011 report, *Clinical Practice Guidelines We Can Trust*, emphasized guideline development group composition and external review.⁵ 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.

Alok A. Khorana, MD

Alex C. Spyropoulos, MD, FCCP
Rochester, NY

Jeffrey Zwicker, MD
Boston, MA

Gary H. Lyman, MD, MPH
Durham, NC

Charles W. Francis, MD
Rochester, NY

Affiliations: From the James P. Wilmot Cancer Center and Department of Medicine (Drs Khorana, Spyropoulos, and Francis), University of Rochester; Division of Hemostasis-Thrombosis (Dr Zwicker), Beth Israel Deaconess Medical Center, Harvard Medical School; and Duke University and Duke Cancer Institute (Dr Lyman).

Funding/Support: Dr Khorana is supported by grants from the National Cancer Institute [K23 CA120587]; the National Heart, Lung, and Blood Institute [R01 HL095109]; and the V Foundation. Drs Lyman and Francis are supported by the National Heart, Lung, and Blood Institute [R01 HL095109]. Dr Lyman is also supported by the National Cancer Institute [RC2 CA148041].

Financial/nonfinancial disclosures: The authors have reported to *CHEST* the following conflicts of interest: Dr Zwicker has received funding support from Sanofi-Aventis US LLC. Dr Lyman is co-chair and Drs Khorana and Francis are members of the American Society of Clinical Oncology VTE Guidelines Panel. Dr Francis is a member of a steering committee for a study sponsored by Eisai Co, Ltd, and participates in a registry sponsored by Eisai Co, Ltd. Dr Spyropoulos has reported that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

Correspondence to: Alok A. Khorana, MD, 601 Elmwood Ave, Box 704, Rochester, NY 14642; e-mail: alok_khorana@urmc.rochester.edu

© 2012 American College of Chest Physicians. Reproduction of this article is prohibited without written permission from the American College of Chest Physicians. See online for more details.
DOI: 10.1378/chest.12-0423

ACKNOWLEDGMENTS

Role of sponsors: The sponsors had no role in the design of the study, the collection and analysis of the data, or in the preparation of the manuscript.

REFERENCES

1. Kahn SR, Lim W, Dunn AS, et al. Prevention of VTE in nonsurgical patients: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012; 141(2)(suppl):e195S-e226S.
2. Amir E, Seruga B, Niraula S, Carlsson L, Ocaña A. Toxicity of adjuvant endocrine therapy in postmenopausal breast cancer patients: a systematic review and meta-analysis. *J Natl Cancer Inst*. 2011;103(17):1299-1309.

3. Hurwitz HI, Saltz LB, Van Cutsem E, et al. Venous thromboembolic events with chemotherapy plus bevacizumab: a pooled analysis of patients in randomized phase II and III studies. *J Clin Oncol*. 2011;29(13):1757-1764.
4. Khorana AA. Risk assessment and prophylaxis for VTE in cancer patients. *J Natl Compr Canc Netw*. 2011;9(7):789-797.
5. Graham R, Mancher M, Wolman DM, Greenfield S, Steinberg E, eds; Committee on Standards for Developing Trustworthy Clinical Practice Guidelines; Board on Health Care Services; Institute of Medicine of the National Academies. *Clinical Practice Guidelines We Can Trust*. Washington, DC: National Academies Press; 2011.

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 Grading 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 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