Deep Vein Thrombosis Prophylaxis

To the Editor:

We appreciate the comments made in a recent issue of CHEST (February 2009) by Eikelboom et al about the American Academy of Orthopaedic Surgeons (AAOS) clinical practice guideline “Prevention of Symptomatic Pulmonary Embolism in Patients Undergoing Total Hip or Knee Arthroplasty.” The AAOS welcomes continued professional dialogue on the topic of prophylaxis and will consider all such comments when it performs its scheduled update of its guideline in 2010. However, we would like to reiterate that we remain concerned about the use of deep vein thrombosis (DVT) as a surrogate marker for pulmonary embolism (PE), and about the potential in the joint replacement patient for iatrogenic hemorrhage (with its associated complications) that can result from PE prophylaxis.

Part of the difficulty of using DVT as an outcome of choice is that it may not be an outcome that is as important to patients as PE or hemorrhage, particularly when the DVT is asymptomatic. The AAOS represents practicing orthopedic surgeons who are often ambivalent about administering a prophylactic regimen that, in large part, has been validated by its proven ability to lower the risk of asymptomatic DVT. This is not viewed as being an acceptable tradeoff when considering the risk of patient harm associated with major hemorrhage. The common perception is that relatively aggressive attempts to prevent DVT underestimate the risk of bleeding.

To be a valid surrogate measure, a surrogate must meet strict criteria. First, the measure should have a well-established relationship (ie, correlation) with the relevant clinical end point. Eikelboom et al nicely summarized data showing that such a correlation exists between DVT and PE. However, it is also important to note that one has greater confidence in the validity of a surrogate if the correlation is large, and it is not clear that the relative risks presented by Eikelboom et al, which range from approximately 0.3 to 0.5, are, in fact, large.

Furthermore, for a surrogate to be valid, it should also be possible to use the effect of the treatment on the surrogate to estimate the amount of clinical benefit a patient will experience. Eikelboom et al have again presented correlations to suggest that such an estimate can be derived and, again, it is not clear that these correlations are sufficiently large. However, even large correlations are not sufficient to demonstrate the validity of a surrogate, because even a perfect correlation between the treatment-induced effects on a potential surrogate and a patient-oriented outcome does not guarantee the utility of that potential surrogate. Further, summary metaanalytic data, such as those reported by Eikelboom et al, can be misleading. Data that allow for a correct metaanalytic interpretation of the validity of surrogate measures do not appear to be available, but it is worth noting that the desired analysis would involve regressing the effect of an intervention on PE, and also regressing the effect of that intervention on DVT for each trial. One would treat the coefficients from these two regressions as random variables with a joint distribution over all trials. The estimated parameters from this joint distribution would then be used to predict mean PE rates from the expected DVT rates. A correct interpretation of the results of single studies requires similar analytic considerations.

Although meeting these two criteria is necessary to establish a surrogate as valid, meeting these two criteria is not sufficient to establish the surrogate as valid. For a valid surrogate, the treatment effect on the clinical outcome must also be entirely explained by the treatment effect on the surrogate, a criterion known as the "capture criterion." This criterion was not specifically addressed by Eikelboom et al, but others have found that there is insufficient evidence to conclude that DVT meets this criterion.

In the absence of meeting all three of these criteria, we remained concerned about the use of DVT as a surrogate outcome. We are particularly concerned because the use of surrogate outcomes has caused harm to patients. Hemorrhage, which can be fatal, is a noteworthy harm of DVT prophylaxis. Unfortunately, the impact that this harm has on medical decision making was not addressed by Eikelboom et al and, as shown in the AAOS guideline, may occur in 1.8% of all patients who receive systemic prophylaxis. To date, there has been no formal consideration of the tradeoffs between the benefits and the harms of DVT prophylaxis, as might be accomplished with a decision analysis.

At the same time, the AAOS recognizes that having two different guidelines reach different conclusions can be confusing. To resolve this confusion, we would welcome the opportunity to work with the American College of Chest Physicians when we update our clinical practice guideline on preventing PE.

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Response

To the Editor:

We welcome the opportunity to respond to the concerns raised by Zuckerman and colleagues regarding our comparison between the guidelines of the American College of Chest Physicians and those of the American Association of Orthopaedic Surgeons (AAOS)1 for the prevention of venous thromboembolism in patients undergoing major orthopedic surgery.

Zuckerman and colleagues question the validity of deep vein thrombosis (DVT) as a surrogate measure of outcome for pulmonary embolism (PE). They base their opinion on the imperfect correlation between DVT and PE, and on their view that the effects of anticoagulants on the prevention of PE are not entirely explained by their effects on DVT. We accept that DVT is not a perfect surrogate for PE and that PE is the most important outcome for patients. However, we do not accept the complete rejection by the AAOS guideline panel2 of DVT as an important outcome in the setting of venous thromboembolism prophylaxis.

Having said this, it also appears that, despite statements to the contrary, the AAOS tacitly accepts DVT as a valid outcome because they recommend anticoagulant prophylaxis for most patients undergoing elective hip and knee surgery. These AAOS recommendations are made despite a lack of benefit, from their indirect comparisons, for anticoagulant therapy in preventing PE in the observational studies that they cite. Rather than questioning the validity of DVT as a surrogate for PE, the key issue is whether the quality of the evidence that is based on the results of a reduction in the incidence of asymptomatic DVT justifies a grade 1A recommendation or whether it should be downgraded to a weaker recommendation.

The second issue raised by Zuckerman and colleagues concerns the tradeoff between the benefits and harms of thromboprophylaxis. This is a valid concern, because it is not possible to compare the benefits and harms (eg, bleeding) of anticoagulant prophylaxis when the benefits are measured by a reduction in the incidence of asymptomatic DVT. There is, however, overwhelming evidence from randomized, controlled trials that pharmacologic thromboprophylaxis, compared with placebo treatment or no treatment, reduces the incidence of PE in patients undergoing major orthopedic surgery and in other high-risk groups.3–5 We think that all patients undergoing major orthopedic surgery should receive a method of prophylaxis that has been proven to be effective in randomized trials.

We agree with Zuckerman and colleagues that conflicting guideline recommendations are confusing, not only for patients and health-care providers but also for third-party insurers who use guidelines to develop performance measures that influence payment. Closer collaboration between the AAOS panel and the American College of Chest Physicians panel in advance of future updates may help to resolve some of the differences.

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