Response
To the Editor:

We thank Dr Vos and colleagues for providing important additional studies that support the use of long-term azithromycin therapy to treat and, possibly, prevent posttransplant bronchiolitis obliterans syndrome (BOS). These studies should have been included in our review of chronic macrolide therapy in inflammatory airways disease1 but were not available at the time of submission.

Their recently published retrospective observational study2 is the largest to date and confirms previous findings that a dichotomy exists in the clinical spectrum of BOS, with neutrophilic allograft dysfunction being macrolide responsive, whereas fibroproliferative BOS is not. Importantly, their study supports the finding observed by Jain et al3 showing better long-term survival in responders compared with nonresponders. Given these more recent studies, we wish to change our grading recommendation to 2A in favor of the use of long-term azithromycin therapy in a subgroup of patients with established BOS (neutrophilic).

We believe that the recently published randomized controlled trial of azithromycin prophylaxis in lung transplant recipients by Vos et al4 is the first to demonstrate that long-term macrolide therapy may prevent BOS. Additionally, this study supports the immunomodulatory effects seen with certain macrolides, even when given at low doses, as discussed in our review. We agree that this is good evidence supporting the use of long-term, low-dose azithromycin therapy to prevent BOS. However, additional placebo-controlled randomized trials are necessary to further define the potential adverse effects of this therapy.

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References

Assessing the Performance of the HAS-BLED Score
Is the C Statistic Sufficient?
To the Editor:

I read with interest the article by Pisters et al1 in CHEST (November 2010) that addresses the problem of major bleeding in patients with atrial fibrillation during treatment with oral anticoagulant drugs. The authors suggest a new user-friendly score in order to assess the risk of major bleeding and, possibly, to support clinical decision making about antithrombotic therapy in patients with atrial fibrillation. They evaluated the predictive accuracy of the model by using the C statistic. Although the C statistic should offer a simple and intuitive measure of the accuracy of predictions using a single test, several readers might not be so familiar with it. Conventionally, the evaluation of a new scoring system is performed using calibration, discrimination and, to a lesser extent, classification measures (mainly sensitivity and specificity), and likelihood ratios.2,4

The calibration is generally assessed with the Hosmer-Lemeshow goodness-of-fit test,3 which is a summary measure of the model’s ability to predict outcome for groups of patients having different levels of risk. Patients are rank-ordered according to outcome probability; they then are divided into deciles of risk. Expected and observed outcomes are compared within each decile of risk. The results of comparisons for each cell of the contingency table are summed, and that result is compared with the χ²-distribution. P values larger than .05 demonstrate adequate model calibration across the entire range of risks.

On the other hand, discrimination is commonly evaluated using the area under the receiver operating characteristic curve.3,4 The area under the receiver operating characteristic curve summarizes in a single number the overall discrimination across the range of risks, independently of disease prevalence and without loss of information due to the choice of a particular decision criterion, as happens for classification measures.2,3 The area can range from 0.5 to 1.0; 0.7 is considered the minimal value acceptable in the validation of a model. Finally, although the role of classification measures in the assessment of the performance of scoring systems has been questioned,2,3 most readers are familiar with these measures, particularly with sensitivity and specificity. In my opinion, such an interesting article could have benefited if the authors had reported in a table at least some of the above-mentioned time-honored statistics, making easier the interpretation of the performance results of the model, as well as its comparison with other scoring systems.

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Financial/nonfinancial disclosures: The author has reported that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

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Response

To the Editor:

Dr Corbanese raises the question as to whether the C statistic suffices as a comprehensible measure of predictive accuracy of our novel bleeding risk model, HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly [> 65 years], drugs/alcohol concomitantly). We acknowledge that the C statistic has its shortcomings, although it is used widely in many validation studies of risk-scoring systems. In addition, the moderate size of the Euro Heart Survey study population1 was reason not to apply the complex statistics proposed by Dr Corbanese in our analysis.

However, in a recent second validation of HAS-BLED, Lip et al2 tested the different statistical methods on the available bleeding risk models in a much larger clinical trial cohort (> 7,000 patients). In this study, univariate Cox regression was used to estimate the hazard ratios and 95% CIs for individual risk factors, with major bleeding as the dependent variable. All potential risk factors investigated in the univariate analyses were included in the multivariate Cox regression analyses; only those variables with P values that remained significant at the 5% level in the presence of other selected variables were retained in the final model. Then, C statistics were estimated to quantify the predictive accuracy of the risk schemes, with 95% CIs obtained by bootstrapping analyses.

The Hosmer-Lemeshow test for calibration was also performed by Lip et al in conjunction with all C statistics, and none of the P values was ≤ 0.05 for any of the risk scores (ie, lack of goodness of fit was not indicated). For HAS-BLED in particular, the P values were .24 for all patients and .13 for the warfarin patient cohort. Furthermore, using multivariate Cox regression models, Lip et al2 tested whether the HAS-BLED score added significantly to models already incorporating the four older scores, one at a time. In all four instances, HAS-BLED was associated with predictive improvement when inserted into models already incorporating the older scores. In contrast, none of the other four older scores added significantly when inserted one at a time into a model already including HAS-BLED. Thus, we hope we have clarified the interpretation of the predictive accuracy of the HAS-BLED model, as well as its comparison with the other bleeding risk models, in the second validation study, which had a much larger sample size and used other statistical methods beyond the C statistic,2 as suggested by Dr Corbanese.

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Financial/nonfinancial disclosures: The authors have reported to CHEST the following conflicts of interest: Dr Pisters has consulting fees from Bayer and Boehringer Ingelheim and lecture fees from Boehringer Ingelheim. Dr Lane is the recipient of an investigator-initiated educational grant from Bayer Healthcare and has received sponsorship to attend the European Society of Cardiology Congress 2009 from AstraZeneca. Dr Crijn has received consulting fees from Boehringer Ingelheim, Sanofi- aventis, and AstraZeneca; grant support from St. Jude Medical, Boston Scientific, Boehringer Ingelheim, Sanofi-Aventis, Medapharma, and Merck; and honoraria from Medtronic, Sanofi-Aventis, Medapharma, Merck, Boehringer Ingelheim, and Biosense Webster. Dr Lip has served as a consultant for Bayer, Astellas, Merck, AstraZeneca, Sanofi-Aventis, Axy, Portola, Biotronic, and Boehringer Ingelheim, and has been on the speakers bureau for Bayer, Boehringer Ingelheim, and Sanofi-Aventis. Dr Nieuwlaat has reported that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

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DOI: 10.1378/chest.11-0184

REFERENCES


The HAS-BLED Score and Renal Failure

To the Editor:

In a recent issue of CHEST (November 2010), Pisters et al published an interesting work that establishes a score to assess 1-year risk of major bleeding in patients with atrial fibrillation. In this article, kidney failure (defined as the presence of chronic dialysis...