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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 INR, elderly, 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 population 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 al 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 ≤.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 al 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, as suggested by Dr Corbanese.

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The HAS-BLED Score and Renal Failure

To the Editor:

In a recent issue of CHEST (November 2010), Pieters 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...
or renal transplantation or serum creatinine ≥ 200 μmol/L) is identified as a risk factor for major bleeding. The “Discussion” section of the article stated that in the vast majority of patients with atrial fibrillation who require oral anticoagulation (CHADS₂ [congestive heart failure, hypertension, age > 75 years, diabetes mellitus, previous stroke/transient ischemic attack (doubled)] index ≥ 2), the risk of bleeding outweighs the potential benefits of oral anticoagulation if the HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly [> 65 years], drugs/alcohol concomitantly) score exceeds the individual CHADS₂ index. As such, a 75-year-old man with hypertension and renal failure would have a CHADS₂ index of 2 and HAS-BLED score of 3, and the oral anticoagulant treatment should be discouraged. We believe that this recommendation does not take into account the impact of renal failure on thromboembolism in patients with atrial fibrillation. In all trials in which the benefit of oral anticoagulant in the prevention of thromboembolism in atrial fibrillation was established, the patients with end-stage renal failure were excluded, and in the European Heart Survey on atrial fibrillation, renal failure was not evaluated as a risk factor for thromboembolism. However, in the ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) study, chronic kidney disease increased the risk of thromboembolism in atrial fibrillation independently of other risk factors; in addition to this, studies carried out in our institution show that the patients with end-stage renal disease and atrial fibrillation have a very high rate of thromboembolism. We believe that this excellent risk score should have considered that although renal failure can increase the bleeding risk, it can also increase the risk of thromboembolism.

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Response

To the Editor:

We thank Drs Vázquez and Sánchez-Perales for their interest in our recent article in CHEST (November 2010). We would like to emphasize our mutual agreement on the importance of chronic kidney failure (defined as the presence of chronic dialysis or renal transplantation or serum creatinine ≥ 200 μmol/L) as a thromboembolic risk factor, as was highlighted in the article by Go et al on the importance of decreased glomerular filtration rate and proteinuria as risk factors for stroke.

However, patients with chronic kidney failure represent a difficult treatment problem. Not only are these patients at high risk of thromboembolism, but they are also at high risk of bleeding, myocardial infarction, vascular events, and all-cause mortality. That the Euro Heart Survey on atrial fibrillation (AF) did highlight the absence of definitive evidence on chronic kidney failure or proteinuria is a limitation, as we did not have information on proteinuria in our survey. Nonetheless, patients with severe chronic kidney failure have not been adequately studied in clinical trials of stroke prevention in AF, and our proposal of using the HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly (> 65 years), drugs/alcohol concomitantly) score was meant to provide a simple, user-friendly score for use in everyday clinical practice that would be applicable for the majority of patients with AF. Indeed, one could informally apply an unwritten rule for guideline writing: that any recommendations need to be applicable for > 80% of the time, in > 80% of the patient population.

Drs Vasquez and Sánchez-Perales challenge our discouragement of the use of oral anticoagulation if the HAS-BLED score outweighs the CHADS₂ (congestive heart failure, hypertension, age > 75 years, diabetes mellitus, previous stroke/transient ischemic attack [doubled]) score. Balancing the risk of stroke and bleeding solely based on this simplistic subtraction is tricky and fails to take into account significant (and important) differences in morbidity, mortality, and associated costs within the different types of major bleeding and compared with AF-related ischemic strokes. Indeed, a high HAS-BLED score is indicative of the need for caution and/or regular review of patients following the initiation of antithrombotic therapy, rather than the complete nonuse of oral anticoagulation.

Despite the awareness of the above-mentioned shortcomings of our proposed “rule,” we strongly believe its use is justified. Compared with a scenario in which no practical guidance on balancing stroke and bleeding risks in patients with AF is available, large numbers of patients are automatically deemed unsuitable for oral anticoagulation. Given that poor guideline adherence has a significant impact on adverse outcomes, undertreatment can be reduced by applying decision rules, at the cost of a few cases in which oral anticoagulation may be withheld.

With regard to the scenario illustrated by Vázquez and Sánchez-Perales of a 75-year-old man with renal failure and hypertension, a history of hypertension is less of a risk than uncontrolled hypertension, in relation to bleeding. With the age of 75 and the presence of renal failure scoring, the patient’s HAS-BLED score is 2. As his CHADS₂ score is also 2, application...