Does β Selectivity Really Affect Outcome?

To the Editor:

We read with great interest the October 2013 article1 entitled “Selective β1-Antagonism with Bisoprolol is Associated with Fewer Postoperative Strokes than Atenolol or Metoprolol,” where the authors describe a decrease in the risk of stroke in patients receiving bisoprolol versus those receiving the less selective β-antagonists, atenolol and metoprolol. Although the results are noteworthy, it remains unclear to us that the outcomes reflect relative β selectivity. Previously published studies have demonstrated an association between the time of initiation of β-blocker therapy and outcome, with higher morbidity and mortality being associated with the initiation of β-blockade nearer the time of surgery. Flu et al.2 showed significantly fewer cardiovascular events as well as significantly lower mortality in patients who were initiated on β-antagonists more than 1 week preoperatively compared with that in patients who were initiated on β-antagonists less than 1 week before surgery. Ellenberger et al.3 in a 2011 issue of Anesthesiology, a study in which the author of this article was an active participant, similarly described worse outcomes in patients receiving acute β-blockade in comparison with the outcomes in patients receiving chronic therapy. In this current study, the authors note the lack of evidence of β-blocker usage in 35% of their patients before hospitalization, which was consistent with their previous data demonstrating that approximately 30% of their patients were started on β-antagonists between the time of admission and surgery. Unfortunately, they failed to quantify in the published article whether metoprolol, atenolol, and bisoprolol usage were proportionately similar in this higher-risk group. One may speculate or perhaps even assume that in anticipation of the need for intravenous β-blocker therapy perioperatively, these 30% of patients, whose outcomes are predictably worse, would be much more likely to receive either metoprolol or atenolol. Both of these have an intravenous formulation; bisoprolol does not. The authors even comment that only a small number of patients received more than one of these drugs, suggesting that our assumption is in fact correct. With this as a premise, we wonder whether this bias for initiating therapy near the time of surgery with metoprolol and atenolol versus bisoprolol was the reason behind the higher stroke rate and not differences in cerebral blood flow occurring as a consequence of β-receptor selectivity. Fortunately, the relative effects of β selectivity versus time of initiation could be clarified either by removing all patients not on chronic therapy from the analysis or by demonstrating no relation between time of initiation of β-blocker therapy and choice of medication.

Furthermore, in this published study, the average dosages of β-blockers given are not noted. This is relevant because the PeriOperative ISchemic Evaluation (POISE) study4 demonstrated that hypotension secondary to metoprolol was associated with an increased incidence of stroke. In the POISE study, the dosages of metoprolol given were relatively high. In contrast, Wallace et al.5 demonstrated that lower doses of metoprolol proved to have better outcomes, so a comparison of the relative doses of β-blockers may be relevant.

Finally, one can just as easily speculate that metoprolol’s variable metabolism, which may result in relative overdosing or underdosing, may be the cause of the differences and not its β selectivity.6

Although we have concerns that this study does not truly demonstrate the advantages of β selectivity, others have demonstrated improvements in outcomes with bisoprolol when given well before the perioperative period.7 Also, as demonstrated in this study, Wallace et al.5 have also noted the relative advantages of atenolol versus metoprolol. Many have assumed that these differences in outcomes were related to the initiation of therapy and the variable metabolism of metoprolol. The authors’ suggestion that β selectivity alone may be the source of improvement clearly warrants further investigation.

Competing Interests

The authors declare no competing interests.

Jordan Field Wicker, M.D., David Bronheim, M.D.
Mount Sinai School of Medicine, New York, New York (D.B.). david.bronheim@mountsinai.org

References

In Reply:
We wish to thank Drs. Wicker and Bronheim for their interest in our recent publication and welcome the opportunity to address their concerns. They question whether the impact of early initiation of β-blocker may have confounded our analysis. This is entirely appropriate because it is possible that metoprolol is preferentially used in acute administration, a population that has been shown to be associated with increased cardiovascular outcomes.

First, we would point out that our recent article was not simply arrived at through a data-mining process but carried out to investigate a specific hypothesis: β-receptor selectivity increased stroke rates. Our hypothesis was firmly based on the physiologic changes that we had observed in several previous animal studies. These experimental investigations, started in 2005, were on the basis of several signals that we had observed in both animal models of stroke and a meta-analysis of non-cardiac surgical patients. Thus, with publication of our recent article, there are now both physiologic rationale and human data supporting the THESIS that β selectivity is one of the several possible mechanisms mediating the increase in stroke rates with β receptor antagonists. It is also irrefutable that perioperative β-receptor antagonism is a major patient safety issue.

Although we think that the issue of timing is an important component of β-blocker safety, we do not believe that it is the primary reason behind the increased incidence in β-blocker–mediated perioperative stroke. The issue of timing has been addressed now in at least five different articles, all using separate databases, and varied outcome measures, outcomes that are not equivalent. The first report, Flu et al. used data from Erasmus Medical Centre. This group and its data resources are currently the object of intense scrutiny. In this article, the only outcome that was different at 30 days was an increased rate of detectable troponin T. Ellenberger et al. showed a difference in number of patients with detectable troponin I. Neither of these studies used the universal definition or screened for myocardial infarction. In addition, neither report show a difference in 30-day mortality rates. More recently, London et al., using the Veteran Affairs Surgical database, could not show a difference in mortality based on the initiation within the 7 days compared with those initiated within 30 days of surgery (table 15). Wijeysundera et al. have shown that early versus late initiation of β-blockers is associated with a 50% risk-adjusted increase in mortality. Neither myocardial infarction nor stroke rate (using International Statistical Classification of Diseases and Related Health Problems 10 coding) was shown to be different based on the timing of drug. Importantly, this analysis, using a large administrative database in more than 47,000 Medicare patients, found little difference in the proportion of patients initiating metoprolol or bisoprolol early versus those who were chronically β-blocked (table 2 in reference 1). Thus, our data do not support the idea that metoprolol is preferentially the drug used clinically in acutely starting perioperative β-blockers. In addition, the cumulative data, in these five reports, do not support the notion that timing is important to postoperative stroke.

Third, we also agree that a discussion relating to the dosage of β-blockers is relevant. However, Drs. Wicker and Bronheim are mistaken, the dosages of the three major β-blockers were presented (see line 1 of table 1 in reference 1). The median outpatient dosages found in our population reflect the package insert instruction for use of these β-blockers as antihypertensive and antiangina medications. The variability in dose we present reflects what we consider to be the advantage of chronic dosing: that is, dose titration. Moreover, the doses in our study are identical to the outpatient dosages of metoprolol found in the Wallace study. We would also point out that the higher the dose of a β-blocker the less likely it would be for the drug will maintain a relative β1 selectivity.

As we state in the original article, we agree entirely that this thesis should be subject to further investigation, preferably using a blinded randomized design. Our analysis was intended, and we think reconfirms the possibility that, the physiologic phenomena we demonstrated in animal models of stroke may be active in humans. We are actively seeking support for this proposed randomized trial and invite all interested parties to contact us to get involved in this important investigation.

Competing Interests
The authors declare no competing interests.

Catherine Ashes, M.D., Saul Judelman, M.D., Duminda Wijeysundera, M.D., Ph.D., Gordon Tait, Ph.D., Gregory M. T. Hare, M.D., Ph.D., C. David Mazer, M.D., W. Scott Beattie, M.D., Ph.D. University of Toronto, Toronto, Ontario, Canada (W.S.B.). scott.beattie@uhn.ca

References

Anesthesiology 2014; 120:1277-99

Table 2 in the referenced article suggests that stroke is also different; however, there were five strokes in the early group and two strokes in the late group, which displays a fragile result.