With the publication of the POISE study the controversy over perioperative beta blockade (PBB) has intensified to what many would consider a critical “boiling point” leading to complete polarization between proponents and opponents (Red vs. Blue?). (1) The results of the only “mega-trial” in this arena would appear to place the clinician (and the patient) in an untenable position. “Aggressive” PBB, although associated with a significant reduction in perioperative MI (and several other related outcomes) came at what appears to be an unreasonable compromise, namely a significantly increased rate of stroke and noncardiac death (primarily related to sepsis/infection). The reduction in PMI, although quite convincing from a statistical standpoint with a treatment effect similar to the reduction in reinfarction rates associated with longterm beta blocker therapy in medical patients (and not the hard to believe 90% treatment effect reported initially by Poldermans in his small DECREASE 1 study), was primarily driven by relatively asymptomatic PMI’s likely related to the mandatory 3 day perioperative surveillance strategy in the protocol. It is unclear how many of these PMI’s fall under the rubric of “troponin spillage” but until further data are published (which is inevitable) it would appear that this is a possibility. In contrast, the strokes that occurred, although of much lower incidence, were clearly associated with greater infirmity and it goes without saying that the deaths appear to be quite permanent. That being said the “wildcard” at play here is the issue of longterm outcomes (the reported outcomes were 30 day). Several prior perioperative studies strongly suggests that troponin spillage is associated with adverse longterm outcome (whether this is simply a marker of greater burden of illness or the actual cause remains controversial). (2,3) Thus, it is quite possible that the balance of efficacy could possibly be in favor of PBB in the POISE study, but we will have to wait until those results are in (and if it is so, it is a bit of a bitter pill to swallow if indeed the
price for some is stroke and death!). The POISE study has engendered a range of visceral responses and in this lecture I will present my interpretation of these responses and attempt interject some clinical science into them. It should be noted that at the time of this writing, the latest updated version of the AHA/ACC Focused Update on Perioperative Beta Blockade was still under revision and review. No doubt the internal debate within the AHA/ACC Group and comments from externals reviewers will be influential in deciding the “fate” of PBB in clinical practice.

To add further fuel to a volatile mix, abstract data was presented in September by Don Poldermans, a strong proponent of widespread PBB, at the European Society of Cardiology Annual meeting. He reported on the findings of the DECREASE IV study, the protocol of which was first reported in a methods paper in the American Heart Journal in 2004. (4) The results of this study, which randomized combinations of bisoprolol and fluvastatin, in 4 treatment arms, demonstrated strong efficacy of both bisoprolol and fluvastatin. In fact, the treatment effects were so strong that the study was terminated well short of its target enrollment of nearly 6,000 patients presented in the methods paper with only 1100 patients. This is similar to what happened in the initial DECREASE study with only 110 patients (all with positive DSE tests) (5) which along with the Mangano atenolol study(6) launched widespread implementation of PBB in many countries (and some critics point to literature claiming that clinical trials terminated early for strong efficacy tend to have higher rates of being refuted later). (7) Thus, it would appear we are still at complete loggerheads on this topic.(8)

As one who was involved in a close, but not quite close enough attempt to launch a large scale cooperative study in the Dept. of Veterans Affairs system in early 2002 (shot down at the very last hurdle), I have a few personal perspectives that I think can shed a bit of light on this controversy. (9) Indeed, given that POISE had just started enrolling its first patients at that time, I was required by VA Cooperative Studies to contact the executive committee of POISE and discuss potential areas of overlap since the VA was not interested in spending a large amount of money (over 10 millions dollars was our target) if the Canadians were able to do it for us (American ingenuity at work!). My communications with them were quite enlightening and we decided early on that there were procedural issues that we did not want to mimic (in fact the controversial dosing
scheme was one of them but we had reasons somewhat different from the opinion of vocal opponents that POISE grossly overdosed their patients) and there other issues that we would not be able to mimic (most notably conducting a true randomized placebo controlled trial given that the fervor and zeal with which PBB was accorded in 2002 made it likely that any such attempts would be rejected by an IRB in this country). So what do we have in 2009? Well the VA has no decent data on which to base its treatment decisions involving millions of patients, instead having to go by the results of a study conducted in a wide variety of different health care systems in populations very different from the average VA patient. A real irony is that it now would likely be impossible to get a PBB RCT through an IRB now for the opposite reasons (eg. fear of excess morbidity and mortality) as in 2002.

After analyzing this area for over a decade and critically studying beta blockers since the time of the introduction of esmolol into clinical practice in the mid 1980’s, I’m now convinced that the failure of organizations/thought leaders in perioperative medicine to articulate some of the obvious physiologic and epidemiologic realities associated with PBB are responsible for the “problems” we have now. (10) If I had to summarize the cardinal error, I would say that a failure to rationally delineate the spectrum of pathophysiology characterizing relatively distinct patient subgroups undergoing a wide variety of surgical procedures involving varying degrees of “stress” was a major factor. Casting too wide a net too quickly with a “one pill fits all” approach led to what may be an irreversible retreat from PBB and rational attempts to sort the good from the bad. Clearly different subgroups of patients are at risk to sustain cardiac damage due to excessive adrenergic tone and responses to them, a classic example would be a patient with known CAD, HTN, normal EF, impaired endothelial function from perhaps diabetes, etc. versus a patient with markedly impaired ventricular function and elevated filling pressures. The first patient is an ideal candidate for aggressive acute beta blockade while the latter is not (although there is no question that longterm low dose use is efficacious). Key variables such as compensatory hemodynamic responses to reduction in oxygen carrying capacity (particularly hematocrit) in which heart rate may at times be the sole factor allowing an increase in oxygen delivery at a point where stroke volume is maxed out, were not properly factored into the equation on the grand scale. Another
major issue is the failure to factor in the observation that all of the physiologic research on beta blockers heart rate response to known levels of standardized exercise protocols as the measure of efficacy. Thus, simply looking at resting heart rate is considered an imprecise measure at best when attempting to predict the response of a patient to “stress”. The pharmacokinetics and dynamics of different beta blockers and along with that pharmacogenomic issues related to the “set point” of the adrenergic receptor itself and the genetic issues related to drug disposition (of which variable plasma levels of metoprolol moderated by certain cytochrome P450 enzymes are but one example) have likewise not been given adequate consideration. (11)

Finally, there are some “common sense” cost effectiveness issues that have clearly been lost in the shuffle. The POISE study was roundly criticized for “acutely and aggressively” beta blocking patients (albeit with a “controlled release” drug that point of fact has very different plasma levels from standard metoprolol tartrate) and these opponents now clearly maintain that slow gradual titration of an beta 1 specific oral agent over a number of days before surgery is the “only” way to go (although curiously in a recent editorial it was noted that the initial dose used in DECREASE 1 was reduced by 50% in subsequent studies with no explanation as to why, since none of the publications from that group reported any substantial morbidity related to the therapy!). (12) Now this is all well and good but ignores the reality of how medicine is and likely has to be practiced in many different settings. Simple logistical issues such as access to care and costs of repeated clinic visits prior to surgery must be objectively considered before one applies this “edict” as a measure of quality of care.

In summary, the saga of PBB does seem to illustrate all of the potential traps inherent in evaluating drug efficacy (RCT use) and effectiveness (real world use) and I think we’ve fall into every hole out there. Whether we dig ourselves out and ever come to a group consensus on this issue remains to be seen. The good news is that the common sense use of beta blockers perioperatively (note I prefer this term of BBP instead of PBB!) is one that nearly all well trained anesthesiologists are capable of instituting when necessary and when done in this manner is usually very efficacious and safe. Pushing further than the boundaries of common sense remains quite perilous!
References


