Is the panic about beta-blockers in perioperative care justified?

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Online publish-ahead-of-print 6 February 2014

Controversial issues need proper discussion, both in science and clinical medicine. Sometimes the interpretation of the available data is complex and not suitable for dissemination through the internet.1 We have just experienced such a case with regards to an opinion piece on beta-blockers in perioperative care published in ‘Cardio-Pulse’, which had failed to undergo peer review that is required for opinion pieces, if scientific statements affecting clinical practice are involved.2 Due to the far-reaching conclusions of the authors based on a meta-analysis published by the same authors, bloggers blew their message into the wind immediately.1 Within minutes and certainly within the hour, the possible consequences of their statements grew almost exponentially in blogs.

The editorial office of the European Heart Journal is aware of its responsibility and reacted accordingly: (i) the online version of the article was immediately retracted; (ii) a retraction notice was placed in the next available issue of the printed version; (iii) both part I and the unpublished part II of the article were sent to five senior reviewers of the highest standing; (iv) the comments of the reviewers were sent to the authors and they were offered the opportunity to resubmit a revised and more balanced version on a de novo basis; and finally (v) the Editor-in-Chief informed the author of one of the beta-blocker trials,3 who was heavily criticized in the article, that the European Heart Journal does not support the conclusions of this inadvertently published feature.

We can do harm with best intentions

There is no doubt that clinical research can be erroneous for several reasons.4–6 Recommendations for practising clinicians have to be continuously adapted due to the ongoing adaptation or refutation of previous assumptions, studies, and/or trials. The data itself may be erroneous for a variety of reasons. In principal, this reflects the scientific process, which, with conjectures and refutations,2 progresses over time—errors are not sins, but rather the major force driving scientific progress.

Physicians working with erroneous assumptions or concepts may certainly harm patients, as indicated in this opinion piece. When George Washington, the first president of the USA, woke up with fever and a cough on 13 December 1799, his wife called his doctor, James Craik who prescribed bloodletting, as was common practice at that time.6 As the patient’s condition deteriorated, he repeated these measures. The attempts of his personal physician eventually led to George Washington’s death on 14 December—and yet Dr James Craik was certain that he had done the right thing, although he should have known that, based on William Harvey’s seminal experiments,7 the volume of circulating blood was limited. In modern times, the CAST trial8 showed that physicians can do harm with the best intentions. Similar experiences occurred in the treatment of heart failure.11

Beta-blockers in perioperative care

Currently, we have another debate: are beta-blockers protective, safe, or even harmful when given in the context of perioperative care? There have been nine trials and a huge registry published on this issue. In 1999, Don Poldermans published a highly cited trial in the New England Journal of Medicine9—then considered a landmark trial—that had screened 1351 patients. Of these, 846 were found to have one or more cardiac risk factors and 173 had positive results on dobutamine echocardiography. Fifty-nine patients were assigned to receive bisoprolol and 53 standard care. Bisoprolol 5–10 mg/day was started at least 1 week prior to surgery and continued 30 days after the operation. Bisoprolol reduced mortality from 17% to 3.4% and myocardial infarction from 17% to 0%—this was big news and changed clinical practice.

Then came the POISE trial with patients undergoing non-cardiac surgery using extended-release metoprolol succinate administered 2–4 h before surgery at a dose of 100 mg or placebo, thereafter to be up-titrated to 200 mg for up to 30 days.12 POISE obviously was a much larger trial, enrolling 8351 patients randomized to this beta-blocker or placebo. Fewer patients in the metoprolol group than in the placebo group had a myocardial infarction (4.2% vs. 5.7%), but surprisingly, there were more deaths in the metoprolol group than in the placebo group (3.1% vs. 2.3%). Further, more patients in the metoprolol group than those receiving placebo had a stroke (1.0% vs. 0.5%). Obviously, this was hard evidence, but it has to be remembered that quite a large dose of a beta-blocker had been used. This may have led to a reduction in blood pressure and heart rate to an extent that did harm.

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There were additional smaller studies, but the field was truly driven by these two randomized trials, which were not concordant—the community was confused at a higher level. Nevertheless, the ESC Guidelines on Perioperative Care published in 2009 recommended the use of beta-blockers under these circumstances.

**What about the Guidelines?**

Then came a thunderstorm: Don Poldermans was fired for committing scientific misconduct on 16 November 2011 by Erasmus University Medical Center, where he had worked for decades and had been head of the perioperative care unit. The question arose as to which of his papers were valid and which ones were not. What about his trial on bisoprolol in perioperative care? What about the ESC Guidelines on Perioperative Care chaired by him? Although the report of the investigative committee of Erasmus University published on 30 September 2012 commented on several aspects of scientific misconduct and on problems with certain publications, to date only one of the manuscripts authored by Poldermans has been formally retracted.

The Editor-in-Chief of the European Heart Journal published an editorial on the issue that coincided with the retraction of the Japanese Valsartan trial. In this editorial, an expression of concern was raised relating to the papers published by Don Poldermans in the European Heart Journal. Due to uncertainty about the validity of his publications, a firm statement was intentionally avoided. In particular, the validity of his bisoprolol trial remained uncertain, as were the ESC Guidelines on Perioperative Care, which were, at least in part, based on this publication. Of note, the report of the Investigative Committee of Erasmus MC, headed by Professor B. Löwenberg, published on 30 September 2012, did not clarify the issue. The New England Journal of Medicine, which had published the article in 1999 had not retracted the report, nor had the committee recommended retraction of this article.

In summer 2013, after a meta-analysis of all trials on the use of betablockers in perioperative care had appeared in Heart, the European Society of Cardiology (ESC) Board reacted together with the American Heart Association and the American College of Cardiology and placed an expression of concern on their websites about their own Guidelines on perioperative care. As announced in their joint statement, the three major cardiovascular societies have in the meantime after a careful analysis of all relevant validated studies, new trials, registries and meta-analyses into their evidence review provided new versions of their Guidelines for Perioperative Care. The one of the European Society of Cardiology has been published recently. Importantly, such a position was reinforced by a recently published registry. In a retrospective cohort analysis evaluating the exposure to beta-blockers on the day of or following major non-cardiac surgery among a population-based sample of 136 745 patients who were matched 1:1 on propensity scores, all-cause 30-day mortality and cardiac morbidity were compared. Overall, 40.3% were exposed to beta-blockers. In the propensity matched cohort, exposure was associated with lower mortality [relative risk 0.73; number needed to treat (NNT) 241]. When stratified by cumulative numbers of the factors in the Revised Cardiac Risk Index, beta-blocker exposure was associated with lower mortality among patients with two factors, three factors, or four or more factors. However, this association was limited to patients undergoing non-vascular surgery. Beta-blocker exposure was also associated with a lower rate of non-fatal Q-wave infarction or cardiac arrest [relative risk (RR), 0.67; NNT 339], again limited to patients undergoing non-vascular surgery. The authors felt that their findings supported the use of a cumulative number of Revised Cardiac Risk Index predictors in decision-making regarding institution and continuation of perioperative beta-blockade.

**What now?**

Are we now confused at a higher level? How can the confusion be sorted out without a proper definitive trial? First of all, we should not jump to conclusions and extrapolate to the population at large as Cole and Francis have done in their meta-analysis and their opinion piece in CardioPulse, which has been retracted by the Editor-in-Chief of the European Heart Journal.

Several aspects must be considered: (i) the dosage of the employed beta-blocker was distinctly different in different trials and registries; (ii) beta-blockers were either given several days before surgery with dose titration or at a high dose immediately before surgery; and (iii) the beta-blocker molecules differed in different trials. All these aspects make it difficult to compare the results in a meta-analysis.

First, a high dose of beta-blockers immediately before surgery may have induced hypotension and bradycardia, explaining the increased stroke and mortality rate seen in POISE, while a more cautious and earlier use of beta-blockers before surgery may have been protective. Interestingly, both the Polderman’s trial and POISE as well as the recent registry found a reduction in myocardial infarction in the patients treated with a beta-blocker. Furthermore, it is possible that different beta-blocker molecules have different effects. In the COMET trial, mortality was reduced with carvedilol compared with metoprolol in chronic heart failure. Thus, many explanations do exist for the discrepancies in the different intervention trials beyond possible fraud in one of them.

The meta-analysis published on 31 July 2013 in Heart identified nine trials enrolling a total of 10 529 patients. Initiation of a course of beta-blockers before surgery was associated with a 27% increase in the risk of 30-day all-cause mortality. In this meta-analysis, the DECREASE family of studies by Poldermans substantially contradicted the meta-analysis of the so-called secure trials as regards the effects of beta-blockade on mortality. Indeed, in the trials considered secure, beta-blockade reduced non-fatal myocardial infarction by 27%, but increased stroke by 73% and hypotension by 51%. The trials not overshadowed by a suspicion of fraud indicated a 27% increase in mortality after the initiation of perioperative beta-blockade, which the guidelines currently recommend. Although methodologically well performed, the limitation of this meta-analysis is the fact that it is mainly driven by the large POISE trial in which a high dose of a beta-blocker was administered immediately before surgery, possibly explaining the higher rate of hypotension, stroke, and overall mortality.

**What do the Guidelines truly recommend?**

The meta-analysis published in Heart, the opinion piece retracted by the editors of the European Heart Journal, and, in particular, the
blogs extrapolate from trials such as POISE the potential harm caused by the currently available Guidelines. Is this appropriate? What do the ESC Guidelines on Perioperative Care really say?

They reiterate the rationale for prescribing beta-blockers in perioperative care, i.e. the catecholamine surge in the perioperative period, resulting in an increased heart rate and myocardial contractility and subsequent increased myocardial oxygen consumption. Further, all trials do show a reduction in myocardial infarction, even those—such as POISE—with an overall increased mortality. Additionally, cardioprotective factors may be the redistribution of coronary blood flow to the subendocardium, plaque stabilization, and an increase in the threshold for ventricular fibrillation.

In terms of beta-blocker usage, the ESC Guidelines of 2009 recommend that treatment onset and the choice of the optimal dosage of beta-blockers should be considered with caution to avoid bradycardia and hypotension. They also highlight the importance of preventing overtreatment with fixed high initial doses as was the case in the POISE trial. Hence, they suggest that the dosage of beta-blockers should be titrated, and that treatment be initiated optimally between 30 days and at least 1 week before surgery (which again differs from the design of several trials, in particular POISE). It is further recommended that treatment should start with a rather low daily dosage, i.e. 2.5 mg of bisoprolol or 50 mg of metoprolol succinate, which should then be adjusted before surgery to achieve a resting heart rate of between 60 and 70 b.p.m. with systolic blood pressure above 100 mmHg. Furthermore, the 2009 Guidelines clearly state that ‘... high dose beta-blockers without titration are not recommended.’ (Class III recommendation).

Thus, the conclusion that the ESC Guidelines could have caused thousands of deaths is based neither on the available evidence nor on the 2009 ESC Guidelines recommendations on dosage and the time of application. Nevertheless, due to uncertainties about the validity of some trials, the statement placed on the ESC website in summer 2013 is certainly appropriate.

What should be recommended in the future?

There are two major issues for practising clinicians. (i) Should beta-blockers be continued in patients already on the drug scheduled for surgery? (ii) Should beta-blockers be started in patients undergoing surgery who have not yet received a beta-blocker? And, if so, which molecule should be selected, at what dose, and how many days prior to surgery? These are difficult, but highly important questions that have been addressed by a task force led by Steen Kristensen and Juhani Knutti that prepared the revised ESC Guidelines on Perioperative Care in close collaboration with their American colleagues which has been published recently. We have to be aware, however, that guidelines are always a consensus of experts in the field and not meant to be laws set in stone. In the meantime, but also with new guidelines at hand, the clinical judgment of experienced physicians remains most important.

Clearly, beta-blockers in perioperative care is an important issue that deserves vigourous discussion. However, what is inappropriate is to jump to conclusions based on uncertain data. Jumping to conclusions may attract attention, but it appears inappropriate for physicians and journalists alike, and may confuse patients, if the scientific basis is still uncertain, as it currently is.

Conflict of interest: The authors of the current viewpoint have neither received honoraria nor research grants related to the use of beta-blockers in pre-operative care.

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