Perioperative β blockade: guidelines do not reflect the problems with the evidence from the DECREASE trials

The trials underpinning initiation of perioperative β blockers in patients with ischaemic heart disease having high risk surgery have largely been discredited, and the remaining evidence points to an increased risk of death. However, changes to the European guidelines have been slow. **Graham Cole** and **Darrel Francis** call for improvements to permit guideline experts to perform rapid amendments when required

Vigorous efforts have been made across Europe to promote use of protocols to reduce perioperative deaths. Since 2009 the European Society of Cardiology (ESC) guidelines have recommended the initiation of perioperative β blockade for patients with ischaemic heart disease or positive preoperative stress test results who are having high risk surgery.[1] This involves giving a short course of oral β blockers from shortly before surgery until a few days or weeks after surgery and is distinct from the long term use of β blockers in heart failure, for which safety and efficacy are well proved. The aim is to reduce perioperative mortality by preventing myocardial infarction. Until 31 July 2014, the recommendation was at the strongest level, class I, which should mean that there is "evidence and/or general agreement that a given treatment or procedure is beneficial, useful, and effective."[1]

The principal support for the recommendation comes from two of the DECREASE (Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography) family of trials, which were discredited in 2011 because of misconduct.[2] Our 2013 meta-analysis of the remaining 11 credible randomised controlled trials indicates that perioperative initation of β blockade increases mortality by 27% (P=0.04, 95% confidence interval 1% to 60%).[3] The ESC did not alter its guidance as soon as the DECREASE trials were discredited in 2011 or after the publication of our meta-analysis reporting an increased risk of death, and in January 2014 we published an opinion article that included a rough calculation, using a formula from ESC experts, of the number of deaths that could result from an effect of this size across Europe. On 1 August 2014 the ESC reduced the strength of its recommendation to class IIb,[4] which means "usefulness/efficacy is less well established" but did not lower it to neutral or negative. We believe this would be appropriate for an intervention that increases mortality.

Here we describe how difficult it has been to challenge and change the guideline and question why the ESC guideline system prevented experts from acting more quickly and downgrading the recommendations further. We also highlight continued reliance on the DECREASE data, despite the guideline's expressed intention to exclude them.[4]

KEY MESSAGES

- European guidelines on initiating perioperative β blockade continue to use trial data that should not currently be taken at face value
- Despite remaining studies showing that initiating β blockade increases mortality by 27%, the European Society of Cardiology could not immediately change the recommendations when problems came to light in 2011
- The August 2014 guideline still gives a positive rather than neutral or negative recommendation and, despite claiming the opposite, still relies on unsound trial data
- Doctors could support the experts developing guidelines by insisting that they are freed to speak out on controversy and have swift pathways for use in emergencies

DECREASE influence

The DECREASE Study Group produced the research that drove the original recommendations and is still cited indirectly through meta-analyses[5 6] in the 2014 guidelines. The group conducted and published a family of six studies, beginning with the DECREASE I trial in 1999.[7] The six studies all have three authors in common and were led by Don Poldermans, then a professor at Erasmus University, Rotterdam, Netherlands. DECREASE I and DECREASE IV are both randomised trials of starting perioperative β blockade in surgical patients.[7 8] The trials showed a large and congruent reduction in mortality that is significantly different from the aggregate of all other trials of this intervention.[3]

Poldermans was appointed chair of the ESC's perioperative task force and oversaw the construction of the guideline covering perioperative β blockers issued in 2009.[1] The first three authors of the guideline were authors of all six DECREASE studies. The bedrock of the recommendations was the two DECREASE trials.[7-9]

In July 2011 serious questions about the integrity of the DECREASE trials led to an institutional investigation by Erasmus University into trials II to V.[10 11] DECREASE I was excluded from that investigation because it was more than 10 years old.[10] In November 2011, Erasmus University publicly reported that the DECREASE trial family was unreliable and contained fictitious data (box 1, see thebmj.com). Poldermans was dismissed for research misconduct.[2]

The inquiry into the DECREASE IV trial of perioperative β blockade found no documentation that any patients had been prescribed a β blocker or that monitoring and up-titration had been done as described.[11] The assessment of outcome events was falsified and the

adjudication committee was fictitious.[11] Cross checking the trial events against the real medical records showed that in a large number of cases the trial outcomes were fictional.[11]

We believe that DECREASE I, too, should be considered insecure, both by association and because of its own red flags (box 2).

Our meta-analysis shows that, without the DECREASE trials, the data on perioperative β blockade show a significant increase in all cause mortality (fig 1).[3] We found a 27% hazard reduction in non-fatal myocardial infarction but a 73% increase in risk of stroke and a 51% increase in risk of hypotension.[3] More good quality data are always welcome, but the significant increase in mortality already visible is not a sound basis for continuing to recommend initiation.

Secrecy

An ESC source who would not be named informed us that guideline signatories are covered by an agreement that events occurring within development of a guideline will be kept "secret and confidential." A secrecy agreement matching this description is accessible online.[16] There seems to be no clause permitting ESC experts to raise the alarm when needed, even to prevent loss of life. It also specifies that signatories "expressly agree that the existence of the Agreement and its whole content are deemed as strictly confidential." Whether there are other such restrictions may therefore never be known.

The ESC issued a press release on 23 November 2011, one week after the DECREASE trials were discredited. It did not rescind the recommendation based on the unreliable DECREASE data. Instead it concluded, "We are saddened by Prof Poldermans' situation and, although we are confident that our guidelines are supported by reliable data, we are carefully looking into the Guidelines for Pre-operative Cardiac Risk Assessment."[17] We need better ways to harness the expert skills of guideline contributors rapidly when source data are discredited.

Guidelines are reviewed every four years.[18] In March 2013 the ESC board agreed[19] that the guideline would be revised and published in summer 2014, effectively giving the 2009 guideline a lifespan of five years.

Our meta-analysis examining the efficacy of perioperative initiation of β blockers was published online in July 2013.[3] The next day the ESC issued a response that it was "currently revising these guidelines as announced in a previous statement in March 2013 taking into account this very complex scientific issue."[20]

By that stage, a new head of the ESC guideline system had been appointed, and told journalists that the ESC was taking the meta-analysis "very seriously" and would "convene an urgent task force to decide whether further actions are required." The urgent task force concluded that decisions should be made on a "case by case basis."[21] The statement did not tell cardiologists that, when insecure data are set aside, there was a mortality increase.

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Box 2 | Concerns about DECREASE I[7 9]

After the 2011 and 2012 Erasmus reports, the ESC press office,[12] *European Heart Journal* leadership,[13] and 2014 ESC guideline[4] continue to rely on DECREASE I as the only trial to reverse the aggregate result of other trials, which is that initiation of perioperative β blockade increases mortality.[3] DECREASE I reports an improbably powerful 91% reduction[7] in death and myocardial infarction. Further details on the concerns below are available in appendix 1 on thebmj.com.

Information missing—When Erasmus University investigated[14] DECREASE I, the patient identities could not be traced for verification of baseline data and outcomes against clinical records. All members of the committee that assessed events and the committee that stopped the trial, named in the *NEJM* paper, now deny having had these roles.[14] The say they did not know they had been named in the *NEJM*. Erasmus could not carry out its planned forensic statistical analysis with the limited information provided by the authors. We suggest that the published papers contain enough meaningful data to decide on the reliability of the reports.

An unusually narrow distribution of heart rate—The range of heart rate of patients at all eight measurement points is so narrow that it is biologically implausible. Each of the eight probabilities is of the order of one in a quadrillion.

Variation between published DECREASE I values and those provided for meta-analysis—Though the values published in the *NEJM*[7] and the values given to meta-analysis[15] might be individually possible, they cannot both be true.

Mathematical uncertainty about the primary endpoint—The odds ratio of the primary endpoint, death and myocardial infarction, is presented[9] with a confidence interval that is mathematically incompatible. Looking more deeply, both seem to be incorrect.

Confusion about which β blocker was used intravenously—The *NEJM* paper makes contradictory statements regarding whether the intravenous agent was metoprolol or bisoprolol.[7]

Several inconsistencies in the tables—These include apparently fractional patients and a patient with minus 1 myocardial infarctions. The inconsistencies cannot be satisfactorily resolved without the raw data.

False hope and a disappeared article

The *European Heart Journal* is the official journal of the European Society of Cardiology. We agreed to write a two part article for the news section of the journal on what readers could do to make clinical research more reliable. The first article explained that the magnitude of harm from research misconduct can be far greater than from clinical misconduct and used perioperative β blockade as an example. The second article presented practical steps to minimise harm from errors in clinical research.

The first article included an estimate of the number of excess deaths that may have occurred as a result of following the ESC guidelines over five years. We calculated this using the peer reviewed formula published in 2004 by the three key DECREASE leaders and guideline authors[1 22] to calculate the effect of perioperative β blockers on numbers of perioperative deaths in one country and applied it across Europe. This formula has not been criticised when used by those authors. Use of the hazard ratio for total mortality from our meta-analysis (1.27) in this formula[3] suggests that there may have been many deaths across Europe if perioperative β blockade was being initiated and was having the effect seen in the credible trials. We reminded readers that the calculation was only one possible estimate but suggested that around half of any resulting harm could have been prevented if practice had changed promptly.

Our first article (appendix 2) appeared online in the journal's CardioPulse section on 14 January 2014. As standard for this section, this was without peer review. But on 16 January friends notified us that all but the title of our article had disappeared (appendix 3). We received a letter from the journal's editor the following day explaining that the article had been temporarily retracted because it needed external peer review.

We believe that the new scientific content was insignificant; it involved multiplying three numbers: the number of operations carried out, their mortality, and the relative risk reduction by not initiating β blockade; a simple formula[22] approved by ESC experts. Eight days after the article was removed from the website, we received reviewer and editor recommendations that included merging the two articles into one. The peer review advised removing the figures and calculation.

If we have been misled by fraudulent data . . . this is a great shame for patients who may have lost their lives

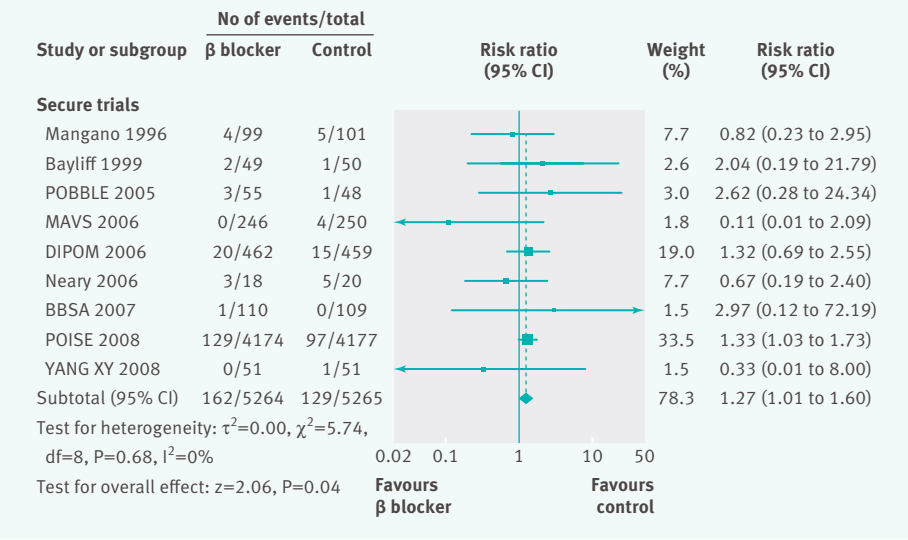
Was the 2009 recommendation ever defensible after 2011?

While our resubmitted manuscript was undergoing review the *European Heart Journal* published, in response, an editorial[13] on 7 February 2014 criticising our disappeared work. It explained that our article had been retracted for peer review, stating that the journal had an absolute requirement for peer review of any item that made scientific statements. The editorial by senior *EHJ* experts certainly made scientific statements, using DECREASE I and introducing observational data[23] to oppose the findings of remaining randomised trials. We hope it was therefore peer reviewed.

The editorial said that "the Editor-in-Chief informed the author of one of the beta-blocker trials, who was heavily criticized in the article, that the *European Heart Journal* does not support the conclusions of this inadvertently published feature." The editorial does not identify the DECREASE author, but, soon afterwards, one of the trial authors became a deputy editor of the journal.[24] Our article did not criticise any author. It was disappointing to read that the journal did not support our conclusion, which was: "With clinical research having far greater potential for harm, our responsibility to rectify errors is all the greater." If peer reviewers did approve the editorial, perhaps they, like everyone else, were unable to read our article (appendix 2) and therefore unable to check facts.

Box 3 | DECREASE I repeatedly escapes notice

- It was excluded from the initial 2011-12 Erasmus investigation because it was older than 10 years[10 11]
- The February 2013 investigation[14] could not identify the patients for verification but was not empowered to take immediate public action
- A published note of concern about Poldermans' articles did not list it,[26] despite his being first author.
- Editorial in the *European Heart Journal* in February 2014 missed a second chance to issue a notice of concern and focused instead on POISE[13]
- The simultaneous ESC statement emphasised that DECREASE I was a "large" study.[12] It accounted for under 1% of the published data from randomised trials[3]
- The 2014 ESC guideline announced that it does not include DECREASE I data,[4] but in fact is included in the recommendations for high risk surgery (via guideline reference 86) and for ischaemic heart disease (via guideline reference 88). DECREASE I and DECREASE IV provide the only events driving the guideline's discussion of the advantages of "targeted heart rate"



Mortality at 30 days in non-discredited randomised controlled trials of initiating perioperative β blockade[3]

A simultaneous press release from the ESC[12] supported the journal's position. It defended the 2009 class I recommendation of perioperative β blockade based on three elements, each of which we consider to be unsound: use of DECREASE I, reliance on a recent observational dataset,[23] and challenging the validity of the POISE trial.[25] It argued for optimism that tweaking dose and timing might reverse the observed increase in deaths.

Our revised article was accepted on 16 June after four rounds of peer review and is awaiting publication.

Use of DECREASE I

The editorial emphasised the DECREASE I approach as reason to believe that perioperative initiation of β blockade might still be beneficial. We do not believe DECREASE I is sound (box 2 and appendix 1). Previously, the journal had issued notices of concern aiming at all articles published by Poldermans as first or last author. The DECREASE I paper in the *European Heart Journal*, which fits this description,[9] was missed.[26]

The notice of concern bemoaned previous failure to recognise arithmetical impossibilities that delayed discovery of misconduct. Ironically, the omitted DECREASE I article is an example of exactly this.

Observational data used to support guidelines

The editorial cited an observational study to support the continued use of β blockade.[23] It is not clear why this observational study should provide more persuasive evidence than the remaining randomised trials, which show increased mortality.[3] Even this observational study could be read as showing an association between β blockers and higher mortality. Superficially, the observational study shows a 40 % higher relative risk of all cause mortality in patients who received a β blocker compared with those who did not (1.4% of 55 138 *v* 1.0% of 81 607 patients, P<0.0001). It does contain a propensity matching process that gives an opposite association, but the published tables contain what seem to be numerous typographical errors and, more importantly, the study is not a randomised controlled trial.

Editorial criticism of POISE

POISE is the largest of the remaining randomised trials in our meta-analysis.[25] The *European Heart Journal* argues that the dose of β blocker in the trial was too large and that this explains why it reduced "heart rate to an extent that did harm."[13] It describes dosing in the DECREASE trials as "more cautious."

POISE and DECREASE used different drug molecules, so milligram comparisons are meaningless. Since the controlled release metoprolol used in POISE has a bioavailability of only 70-75%[27 28] compared with that of immediate release metoprolol, the trial's daily controlled release dose of 100-200 mg is broadly equivalent to 25-50 mg immediate release three times a day, which is a conventional dose. Dismissing the observed mortality increase as merely the result of the dose being "high"[13] or "very high"[12] is not safe. In fact, the POISE regimen reduced heart rate by 7 beats/min,[25] which contrasts with DECREASE I's reported 11-13 beats/min,[7] and DECREASE IV's 12 beats/min.[8] The reductions in heart

rate do not suggest that the dosing used in POISE is excessive.[25]

The *European Heart Journal* said POISE lacked "dose titration."[13] The ESC was concerned it had performed only "uptitration."[12] In fact, the POISE protocol specified that the dose could be reduced.

ESC position for 2014-2018

The ESC issued a new guideline in August.[4] The recommendations are softened to class IIb ("usefulness/efficacy is less well established"), but this is not enough. We believe that the ESC should reduce their recommendation to class III ("not recommended"), to reflect the significant increase in mortality in the credible randomised trials.

We are particularly concerned that it still draws on the DECREASE data, even though it states that it has excluded the trials (box 3). There remains a positive recommendation for starting β blockers for high risk surgery in patients with ≥2 risk factors or an anaesthetic status ≥3, which is supported by three references.[4] Two are not randomised studies. The third uses data from randomised trials but is a meta-analysis subgroup[6] that excludes POISE[25] and includes DECREASE I.[7] The POISE analysis, indicating that higher risk patients seemed most prone to net harm, was not mentioned.[25]

The guidance also gives a favourable recommendation for starting β blockers in patients who have known ischaemic heart disease or myocardial ischaemia, again with three supporting references. Unfortunately, two of them[29 30] turn out to be the same controversial study that "failed to include an analysis by intention to treat and should not now influence perioperative practice."[31] The study omitted in-hospital deaths (which were twice as frequent with β blocker than without),[31-33] and, because it enrolled some patients already on β blockers, it was a mixed trial of initiation of β blockers in some and withdrawal in others. We also missed this second problem, not mentioned by the guideline, when doing our meta-analysis,[3] which perhaps should not have included this trial. The third supporting publication is a meta-analysis[5] that contains four mortality analyses, all of which are comprised only of the same controversial study[29 30] and DECREASE I.[7]

Elsewhere the guideline states that the "benefit of beta blockade was found in five high risk surgery studies," which readers might interpret as five positive trials. When the reference[6] is checked, however, they comprise four trials with neutral results and DECREASE I.

Finally, the guideline states that the benefit of β blockade was found "in six studies using titration to targeted heart rate," which again readers might interpret as six positive results. In fact, four trials had zero events and the other two were DECREASE I and DECREASE IV.[6]

Further action needed

The newly appointed ESC president has declared that "Accountability and transparence will be my key words for Governance. An institution such as ESC needs a very clear Governance model, in order to be effective."[34]

Secrecy during guideline construction is incongruous with this aim. It limits early problem solving and inhibits system-wide learning. Scientific leadership requires clear action to detect fraudulent research and deal with it decisively. The POISE authors set a good example[25 35] by publicly and immediately striking out fraudulent data and making no effort to reassure or express sadness for the situation of fraudulent colleagues. We should all learn from this example.

We believe the ESC guideline system underutilises its most precious resource: the volunteered time of knowledgeable and respected professional leaders. We call for the guideline system to better harness this expertise by permitting them to hold their discussions openly. They must also be free to take urgent corrective action when studies that drive a recommendation are discredited.

If we have been misled by fraudulent data such as those in the discredited DECREASE trials, this is a great shame for patients who may have lost their lives. However, it is a far greater failing to respond incorrectly when the harm is recognised.[36] We need to reinvigorate guideline systems so that experts can act swiftly and openly to prioritise patient safety.

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Contributors and sources: GDC and DPF were trained to initiate perioperative β blockade in eligible patients. DPF taught others to do so. When the DECREASE trial family was discredited for misconduct, GDC and DPF changed their practice and encouraged others to do so. GDC and DPF conceived, wrote, and reviewed the manuscript jointly. DPF is guarantor.

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ALL THINGS CONSIDERED

Stunned resident syndrome

Burnout among first year internal medicine residents is common and well known. It can lead to suboptimal patient care, errors, poor quality of life, and depression. Data on burnout in the first weeks of residency as compared with the remainder of the first year have not been published.

In 20 years of service as head of an academic department of medicine, I have encountered residents who were selected for their overall good performance as students and interns, yet their initial function at the start of their residency programme was almost appalling. With a little practice, they can be spotted easily: their presentations of patients are fumbled; they run around the department with obvious hyperactivity, yet little is accomplished; they actually seem stunned. Thus, residents should never be judged prematurely according to their performance over the first weeks. Just as a myocardium stunned by repetitive episodes of ischaemia may resume full function, a resident stunned by the many new responsibilities and amount of material he or she has to command, may improve given a supportive learning environment and time to adjust.

In my experience, most stunned residents recover within a relatively short time. The steepness of their improvement curve attests to the acuity of their predicament and its high potential of reversibility. Senior hospital physicians need to be more aware of what might be termed "the stunned resident syndrome." Providing a more gentle, gradual, and supportive initiation into the complicated routines of residency might alleviate the problem.

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