Appendix 1 (published as submitted by the author)

The reasons we consider DECREASE I unsound

The 2014 European Society of Cardiology perioperative guideline[i] rates initiation of beta blockade in at-risk patients Class IIb ("usefulness/efficacy is less well established"). Despite being an improvement on Class I, it has still not reached Class III ("not recommended") which would be consistent with POISE,[ii] and the remaining credible trials because their point estimate matches POISE.[iii,iv] This might be because of the influence of the DECREASE I trial which reported an extremely impressive 91% reduction in cardiac death and myocardial infarction. This was published first in NEJM[v] with a follow-up in EHJ[vi] and neither has been retracted.

When the EHJ issued a notice of concern intended to cover all papers led by Poldermans,[vii] DECREASE I was missed[viii] in the journal's search of its own archives.

Erasmus University did not cover DECREASE I in its first investigation (reported in 2011 and 2012) that revealed that, in DECREASE II to VI, the more data that could be found, the more insecure the study seemed (Table 1). The second investigation focused on DECREASE I and was published in July 2014, reporting: [ix]

- No list of participant identities could be found to permit verification against clinical records. (This process had found many events counted in DECREASE IV to be unsupported by the clinical records).

- Apparently there was no surviving copy of the study protocol actually used, despite it being a multicentre RCT. Several aspects of its conduct were not as published.

- For example, the NEJM paper described all events being "evaluated in a masked fashion by members of the adverse events committee" of two named people. They deny being members of it or knowledge of being named in the NEJM paper.

- It also reports that the "significant difference between groups in the incidence of cardiac events prompted the safety committee to interrupt the study". This committee was composed of anther two named people. They too denied participating in a safety committee, analyzing data, stopping the trial, or knowledge of being named in the NEJM paper.

In the document below we lay out our concerns having examined the published claims of the DECREASE I trial. With no way to trace the original data of the patients in DECREASE I, it may not be possible to fully resolve these questions.

I An unusually narrow distribution of heart rate

The 2009 and 2014 guidelines, and the EHJ panic editorial,[x] lay special emphasis on targeting heart rate and frequently cite DECREASE I, directly or indirectly, as grounds for this.

In healthy people heart rate varies from measurement to measurement. Additionally it varies between people. DECREASE I reports the range (minimum to maximum) of heart rate in each arm of the trial at four stages: a total of 8 ranges. Whether each of these ranges is plausible can be judged by calculating the probability that heart rate, distributed as in similar trials, might by chance fall in such a narrow spectrum. Typical standard deviations for perioperative patients can be obtained from other randomized controlled trials of perioperative beta blockade. They are 17bpm[xi], 13.4bpm[xii], 13bpm[xiii], 10bpm[xiv], 15.7bpm[xv], 13.9bpm[xvi],14bpm[xvii] and 12.4bpm[ii]. The smallest is 10bpm.

One range that DECREASE I reports is that the 53 patients in the control group had pre-operative between 72 to 82bpm, i.e. within ±5bpm of a central value. The most charitable probability of a single patient drawn from a distribution with standard deviation 10bpm lying in a range of ±5bpm, is given by $2 * [\Phi(5/10)-0.5]$. This can be calculated in Microsoft Excel using the following formula

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=2*(NORMDIST(5/10,0,1,1)-0.5)
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This comes to 0.383. There are 53 patients in the control group. The probability that an entire group of 53 patients achieves this is $(0.383)^{53}$, which is approximately 10^{-22}.

This probability can be calculated for each of the 8 ranges described in Table 1 of the NEJM paper. All are very small. We therefore consider it implausible that these values truly represent measured ranges of heart rates of patients genuinely enrolled in a trial as described.

In passing we note that the narrowness of the range cannot be explained through the participants being unusually homogenous. Even if the 53 values were a single patient (i.e. a perfectly homogeneous patient group) measured 53 times, 10bpm is an unachievably narrow range of variability. The standard deviation of difference of a pair of standard office measurements of heart rate of one patient on different days is 10bpm[xviii] from which the standard deviation across multiple measurements can be calculated to be $10/\sqrt{2}$ which is 7bpm. The probability of the range of 53 measured heart rates in a single person being within any 10bpm range is $(2 * [\Phi(5/7)-0.5])^{53}$ which is 10^{-15}. The contemporary apex of technical sophistication was an 822-patient study[xix] with complex protocols and sophisticated equipment, which reduced the within-patient standard deviation to 5bpm. We do not consider it likely that DECREASE I had such a setup, since no details were given, and when its sister study DECREASE IV was investigated[xx] there was no evidence of any measurements being made at all. Even if DECREASE I had such equipment and protocols, and even if all the patients were the same person, getting 53 measurements within 10bpm has a probability of $(2 * [\Phi(5/5)-0.5])^{53} = 2\times10^{-9}$ which is still vanishingly implausible.

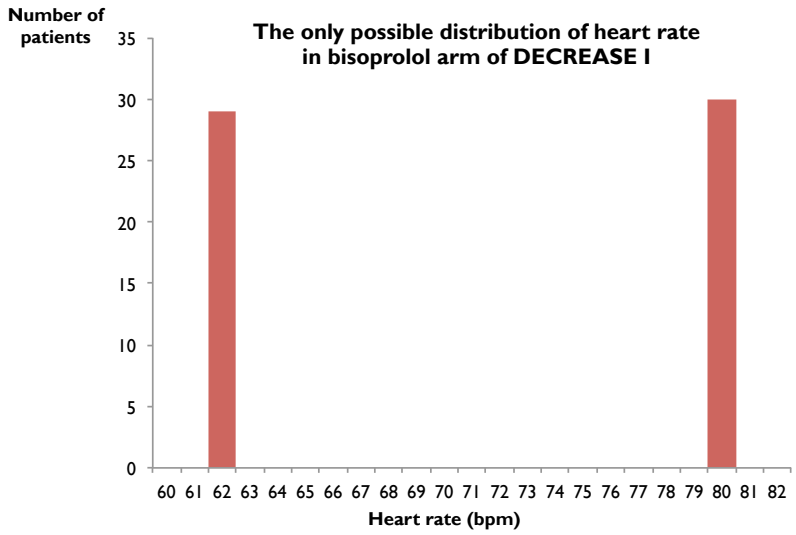
Unresolved biological implausibility of data is recognised as an easily missed early warning of published science later found to be incorrect. When the EHJ editor attempted[xxi] to issue notices of concern on all papers led by Poldermans, he warned everyone to be vigilant for biological implausibility, citing the "embarrassing example" of Darsee's description of a patient aged 17 with children aged 4,5,7 and 8.

2 Variation in DECREASE I values comparing the research paper to the meta-analysis

The DECREASE I investigators reported in their NEJM paper (Table 4) that on the first post-operative day the heart rate ranges were 62-80 in the bisoprolol group and 76-88 in the control group. They also wrote to meta-analysts Biccard *et al.*[xxii] that the standard deviations at that time point were 9.3 and 9.7, respectively. Mathematically it is difficult for the standard deviation to be this large and yet the range so extraordinarily narrow.

For the 59 beta blocker patients, the only distribution that would permit the two statements to be correct would be to have all the bisoprolol patients having their heart rates **at the extremes**, either 62 or 80 bpm. If 29 patients had a heart rate of 62 and 30 patients had a heart rate of 80, the SD would be 9.08. To achieve a SD of 9.3, a few of those at 62 and 80 would require heart rates of 61.5 or up to almost 80.5. The method for measuring heart rate is not reported in DECREASE I but it seems unlikely that such equipment would measure half a heart beat.

The distribution would *have* to look like this (or its mirror image).



The range of heart rate in the control arm is even narrower (76 to 88 bpm). If all the patients were pushed to the extremes, to the greatest extent permitted by rounding (75.5 and almost 88.5 bpm) the SD would be only 6.1 bpm. For the SD to be 9.7, as the DECREASE group informed Biccard *et al*, and for the NEJM paper to be simultaneously correct, appears to us to be mathematically impossible.

A variety of errors could be proposed to explain these discrepancies. For example, the upper limit or lower limit of each range could be incorrect. Alternatively, the Methods section of the NEJM paper does describe calculation of median and interquartile range. It is conceivable that what are repeatedly described as "mean" and "range" might be statistically erroneous terms intended to state "median" and "interquartile range". The opportunity to clarify the situation in the EHJ paper of 2001 was unfortunately missed. Even 15 years later, it would be beneficial for a resolution to be provided.

We therefore do not think it wise to issue recommendations on heart rate titration, monitoring of heart rate, or heart rate targets, based on DECREASE I.

3 Mathematical uncertainty about the primary endpoint

In Table 3 of the EHJ DECREASE I report, the odds ratio for the composite endpoint over the entire period is given as 0.16 with a confidence interval of 0.007 to 0.39.

This is inconsistent. The logarithm of an odds ratio has its confidence interval limits evenly spaced above and below the log of the point estimate. (For example, with 95% confidence intervals, the limits are approximately 1.96 standard errors above and below.) Thus the odds ratio must be equal the square root of the product of its confidence interval limits, but in the example above, it is not.

If one were to look solely at these 3 numbers, there seem to be 3 explanations. Perhaps the lower confidence interval should read 0.07. Perhaps the point estimate should read 0.05. Perhaps the upper confidence interval should read 3.66 (being >1.0, this would invalidate the statistical significance of the result).

We use data in the same table to recalculate the odds ratio is (9/50)/(32/21) = 0.118. The 95% confidence interval comes out to be 0.048 to 0.290.

We do not think this can be explained by the group sizes not being 59 and 53 respectively, and therefore the 50 and 21 in our calculation above being incorrect. The percentages given alongside the numbers 9 and 32 are 15.3% and 60.4% respectively, which can only fit those group sizes.

Table 3, and in particular the primary endpoint result, cannot at present be considered secure.

4 Confusion about which beta blocker was used intravenously

The EHJ editorial supporting beta blockade initiation reports that DECREASE I showed meticulous care with dosing. DECREASE I is currently trusted to be a trial of bisoprolol. The NEJM paper states that 28 out of the 59 beta blocker patients

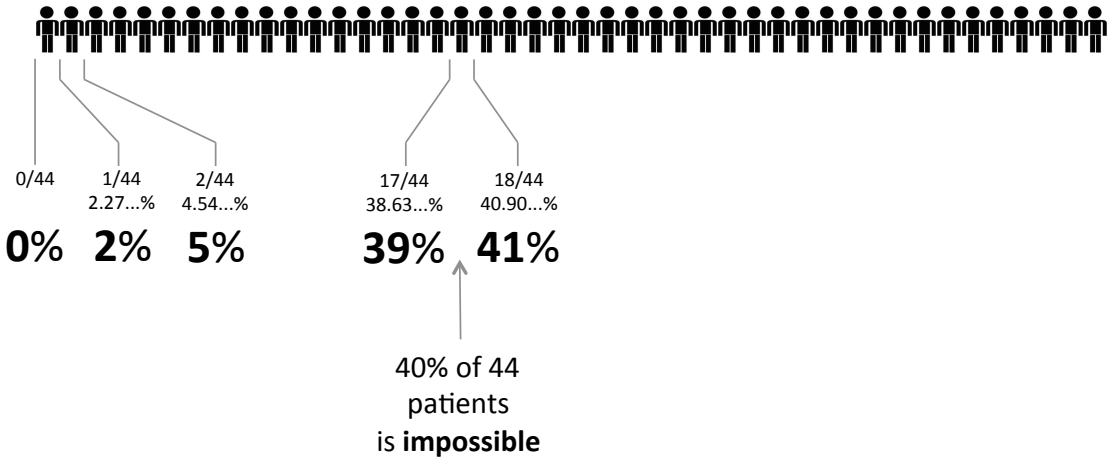
received their drug intravenously in the early postoperative period. In the Results section, it is clear that this drug was intravenous bisoprolol.

The Methods section contradicts this, stating that this drug was "intravenous metoprolol". The methods section does not report the size of the intended intravenous metoprolol doses. Nor does the results section report the amount of intravenous bisoprolol used.

With uncertainty regarding the final protocol and no means to identify patients and check their treatment records, it may be difficult to establish which intravenous beta blocker was actually used. In the sister trial, DECREASE IV, investigation[xx] revealed no documentation that any patient was prescribed any beta blocker.

5 A collection of inconsistencies in the tables

Table 4 of the EHJ DECREASE I report describes a variety of percentages of patients. But some cannot arise from any whole number of patients. For example, 40% of 44 patients is 17.6 patients. Either the percentage or the denominator is wrong.



In the same table, the 23/57 bisoprolol recipients stated to be taking ACE inhibitors at randomisation does not match the 42% stated, nor does the 20/57 stated to be taking aspirin match the 37% stated.

It is possible that the medication status was known for some drugs but not others. There is an error with the numerator, denominator or percentages. If the numerators (23 and 20) and the percentages are both correct, then the denominator would have to be 55 for ACE inhibitors (since 42% can only match 23/55) but would have to be 54 for aspirin (since 37% can only match 20/54). If the numerator patient counts were incorrect 24/57 would indeed by 42% and 21/57 would indeed by 37%. If the percentages might be incorrect, 23/57 would be 40% and 20/57 would be 35%.

Table 1 of the EHJ DECREASE I report[vi] from 2001 describes a group of 57 patients receiving beta blockers. These 57 are a subset of the 59 reported two years earlier

in the NEJM DECREASE I paper.[v] Amongst the 57, the number who had had a previous infarction before enrolment was 33. But amongst all of these, plus two additional patients, the number who had had a previous infarction before enrollment as 32. Both statements cannot be simultaneously true.

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