Analyzing DECREASE trials for extent of data fabrication

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The effect of beta-blockers on perioperative mortality in non-cardiac surgery for patients with coronary artery disease (CAD) has been controversial[1] due to findings of research misconduct in two related clinical trials[2–4]. Three meta-analyses that included the trials subject to research misconduct concluded that beta-blockers decrease perioperative mortality[5–7] whereas a meta-analysis that excluded the suspect trials concluded that beta-blockers increase perioperative mortality[7]. In these studies, perioperative mortality was defined as the deathrate of patients during the period of the surgical procedure, which typically includes admission, anaesthesia, surgery, and recovery.

The trials subject to research misconduct were the Dutch DECREASE-I and DECREASE-IV trials[2–4]. The committees that investigated the integrity of the DECREASE trials reported that data fabrication was likely but that the extent of the data fabrication remained unclear[2–4]. Moreover, the latest guidelines still recommend the usage of beta-blockers in the perioperative period in certain cases[8,9]. Considering these consequences, we aim to estimate the extent of data fabrication in the DECREASE studies[10,11] to further the debate on using beta-blockers in the perioperative period of CAD patients undergoing non-cardiac surgery.

The reports on the integrity of the DECREASE trials primarily focused on the provenance of the raw data but did not investigate the extent to which the DECREASE trials deviated from comparable trials. The provenance is primarily concerned with the origins of the data, verifying things such as (but not limited to) the informed consent and whether data corresponded to patient files. The committee reports did not neglect statistical evaluation however: a statistical expert evaluated the applicability of forensic statistical methods[4] to evaluate results of trials separately (i.e., DECREASE-I, DECREASE-IV). Nonetheless, comparing across trials is a method that has previously been used to monitor trial data quality or to test for potential data anomalies[12]. Moreover, this method has previously proven to be effective in detecting data fabrication[13]. Evaluating the DECREASE trials to other published trials studying the effectiveness of beta-blockers with respect to perioperative mortality could prove informative of the potential extent of the fabrication in the DECREASE trials.

However, the effectiveness of perioperative beta-blockade is obfuscated by both trials afflicted by data fabrication and the type of beta-blocker used in the trial. Various kinds of beta-blockers could vary in their pharmalogical effectiveness with respect to perioperative mortality, and anomalies in the effectiveness of the DECREASE trials might be due to differences in the beta-blockers used [@] and not purely due to data fabrication (given not all data points can be considered fabricated at this point).

To statistically investigate the evidence of data fabrication in the DECREASE studies[10,11], we took three steps. First, we reproduced the findings from a 2014 meta-analysis[7] that contained sufficient information to estimate the deviation of the DECREASE trials from other published trials on beta-blockers. We also include type of beta-blocker to inspect whether this is predictive of the effect of beta-blockers on perioperative mortality. Second, we evaluated the the probability that the DECREASE trial results occurred assuming no data fabrication. Third, we reversed this assumption and assumed that data fabrication did occur and estimated how many data points would have to be fabricated to reproduce the results of the DECREASE trials, if the other published trials are regarded as estimating the true effect of beta-blockers on perioperative mortality in CAD patients undergoing non-cardiac surgery.

Step 1: reproducing meta-analysis of Bouri et al. (2014)

Methods

To ensure that we used similar analysis procedures as in the 2014 meta-analysis[7], we initially reproduced Bouri et al.'s estimates. This ensured that (1) their results are reproducible and (2) we are using the correct estimates in subsequent steps of our analyses. Using figures 2 and 3 from the original paper[7], we extracted the raw event data for the 2 (control vs experimental) by 2 (event vs no event) design, which we used to recompute the natural logarithm of the risk ratio and its standard error. The extracted event data is available at osf.io/aykeh and our analysis plan was preregistered at osf.io/vnmzc.

We computed the log risk ratio (i.e., log RR) for each study and pooled these using the `R` package `metafor`[14]. We estimated a weighted random-effects model using the restricted maximum-likelihood estimator (i.e., `REML`)[15] to estimate the variance of effects. We used the default weighting procedure in the `metafor` package. When there was a zero-count for a cell (e.g., zero events), 0.5 was added to that cell, as is common in meta-analyses on risk- and odds ratios in order to prevent computational artefacts[16]. The 2014 meta-analysis[7] did not specify the variance estimate used; hence, minor discrepancies between our estimates and the original estimates could be due to differences in the estimation procedure.

Results

We were able to closely reproduce the estimates for the different sets of studies (Figure 2 of the 2014 meta-analysis[7]). Bouri et al. differentiated between the estimates from the non-DECREASE trials and the DECREASE trials. We confirmed the effect size estimates and the variance estimates for both the non-DECREASE- and the DECREASE trials, save for some minor discrepancies due to the estimation method. Table 1 depicts the original and reproduced values for both sets of studies.

Table 1: The original- and reproduced meta-analytic results based on the data provided in the 2014 meta-analysis by Bouri et al.

		Risk ratio	τ^2	Confidence interval
Non-DECREASE	Original	1.27	0	[1.01; 1.60]
	Reproduced	1.28	0	[1.01; 1.62]
DECREASE	Original	0.42	0.29	[0.15; 1.23]
	Reproduced	0.44	0.24	[0.15; 1.23]

Second, we meta-analyzed all studies combined, including a dummy predictor for the DECREASE and non-DECREASE studies to reproduce results presented in Figure 4 of the 2014 meta-analysis[7]. Surprisingly, our results showed stronger evidence against equal subgroups than the original meta-analysis[7] (original: $\chi^2(1) = 3.91, p = .05$, reproduced $\chi^2(1) = 6.12, p = 0.013$). Additionally, the original analyses showed substantial residual heterogeneity ($I^2 = 74.4\%$) whereas we found no residual heterogeneit ($I^2=0\%$). Different variance estimates (e.g., `DerSimonian-Laird` instead of `REML`) did not resolve this difference. We tried to clarify these discrepancies by e-mailing the original authors, but did not receive a response. Nonetheless, the broad strokes of the meta-regression confirmed that the DECREASE trials were the determining predictor for the effectiveness of beta-blockers (including DECREASE: $RR = 0.496$; excluding DECREASE: $RR = 1.28$).

Additionally, and exploratively, we evaluated the predictive effect of the type of beta-blocker used in the trials. The DECREASE trials remain predictive of decreased mortality ($RR = 0.496$), whereas the non-DECREASE trials provide tentative, but uncertain, evidence that atenolol results in lower mortality ($RR = 0.751$). Nonetheless, for other beta-blockers in the non-DECREASE trials, there is still tentative and uncertain evidence that beta-blockers increase mortality (bisoprolol: $RR = 2.973$; metoprolol: $RR = 1.307$; propanolol: $RR = 2.041$). Table 3 shows the meta-regression results in full.

Table 2: Meta-regression results for log(RR), including dummy predictors for DECREASE trials (reference: non-DECREASE trials) and type of beta-blockers used in the trial (reference: atenolol).

	Estimate	95% CI
Intercept	-0.287	-1.317; 0.743
Non-DECREASE		
DECREASE	-1.792	-5.082; 1.498
Atenolol		
Bisoprolol	1.376	-1.996; 4.749
Metoprolol	0.554	-0.504; 1.613
Propanolol	1	-1.642; 3.643

Step 2: evaluating the veracity of DECREASE studies

Based on the non-DECREASE estimates from Step 1, we estimated the probability of obtaining the results in the DECREASE trials. To this end, we assumed that the non-DECREASE trials provide a valid representation of the true effect of beta-blockers on perioperative mortality (similar to Bouri et al.[7]; but see the discussion). The estimated probability is also known as the veracity of the data[17], which indicates the probability of the observed data under a given true effect. We assumed that the non-DECREASE studies estimated the true effect distribution of perioperative beta-blockade on mortality, not perturbed by publication bias due to statistical (non)significance. Publication bias was assumed to not be a problem because a substantial number of nonsignificant effects are included in the dataset (9 of 11 nonsignificant results).

Method

Based on the estimated mean log RR and its credible interval in the non-DECREASE studies, we computed the probability of the observed log RR in the DECREASE trials. The estimates of the non-DECREASE studies were obtained from Step 1, which include the estimated log RR (i.e., 0.25), and its 95% credibility interval as provided by the package `metafor` (i.e., [0.01; 0.484]. The meta-analysis model assumes a normal distribution of population effects with the estimated effect as the mean of the distribution. The 95% credibility interval denotes the bounds of the normal distribution that covers 95% of the density, where the standard deviation is calculated as the distance from the mean to either bound, divided by 1.96. This allows for an approximation of the population effect distribution, as depicted in Figure 1.

Based on the estimated effect distribution from the non-DECREASE trials, we calculated the probability of each DECREASE trial result, or a more extreme result. In other words, we computed the p-value for the hypothesis that the DECREASE studies occurred, assuming the information available from the other trials is informative of the true population effect.

Results

Figure 1 indicates that the DECREASE trials are highly unlikely under the estimated effect distribution based on the non-DECREASE trials. More specifically, the results from DECREASE-I (or more extreme) have a probability of 0 (less than 1 in a quintillion) and the results from DECREASE-IV have a probability of 0 (3 in a billion). This indicates the DECREASE trial results are unlikely to have come from the same population effect distribution as the non-DECREASE trials. Moreover, observing two of such extremely unlikely results jointly, as in the DECREASE trials, is highly improbable, 0. This would therefore indicate that the DECREASE trials are severely different from the non-DECREASE trials.

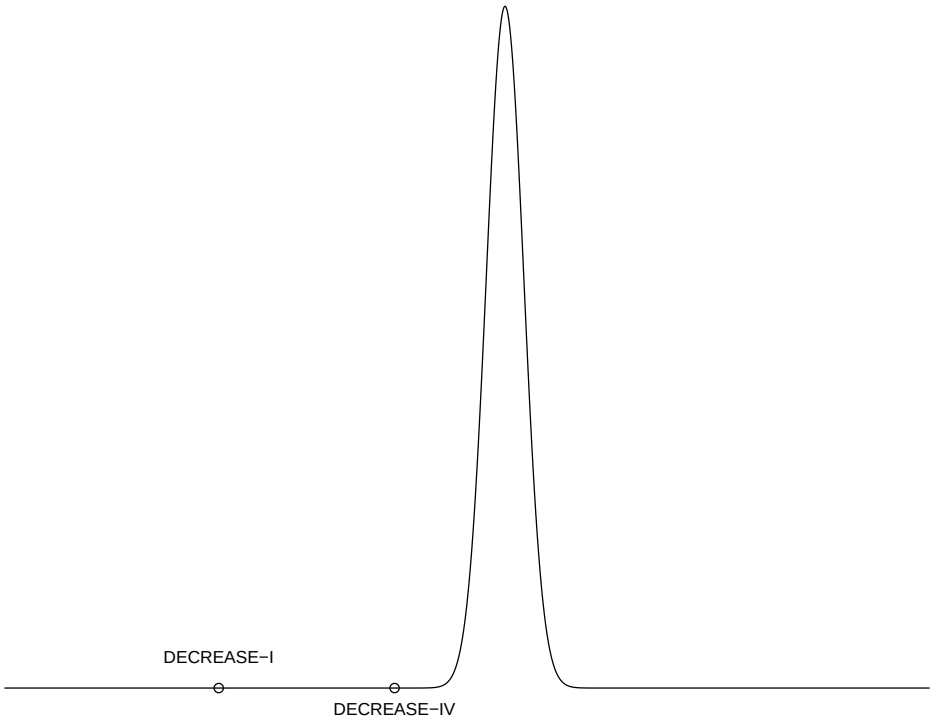

Figure 1: Density plot of the estimated true effect distribution based on the non-DECREASE studies only, with the position of the DECREASE studies highlighted.

Results from Step 1 indicated that no between-study variance (i.e., homogeneity; $\tau^2 = 0$) of the effects was observed; given the small number of studies included (i.e., 9) this estimate is uncertain, however. We conducted sensitivity analyses to see how dependent results are on the heterogeneity estimate. The probability of observing the DECREASE trials stays approximately below 1 out of 1000 until the variance estimate is 0.25; the probability stays approximately below 1 out of 100 until the variance estimate is 0.43 (see Figure 2). To put these numbers into context, a variance of 0.25 would suggest that results of perioperative beta-blockade vary substantially even if perioperative beta-blockade has no effect whatsoever (RRs between 0.779 and 1.284 in 64% of the cases) all due to contextual circumstances of the study.

Step 3: estimating the amount of fabricated data

We estimated the number of data points that would need to be fabricated to arrive at the estimates from the DECREASE trials, given that the non-DECREASE trials represent the true effect of perioperative beta-blockade. In contrast to Step 2 this assumes that the DECREASE trials might in fact contain fabricated data. The estimates from Step 3 provide an indication of the extent of potential data fabrication in the DECREASE studies[2–4,7].

Method

In order to estimate the number of fabricated data points, we first estimated the effect of perioperative beta-blockade on mortality (in log odds) in each trial arm. In total there are four trial arms: one per condition (beta-blocker or control) per trial type (DECREASE- and non-DECREASE trials). For each of these trial arms, we ran a meta-analysis applying the same methods used in Step 1. For each of the two DECREASE

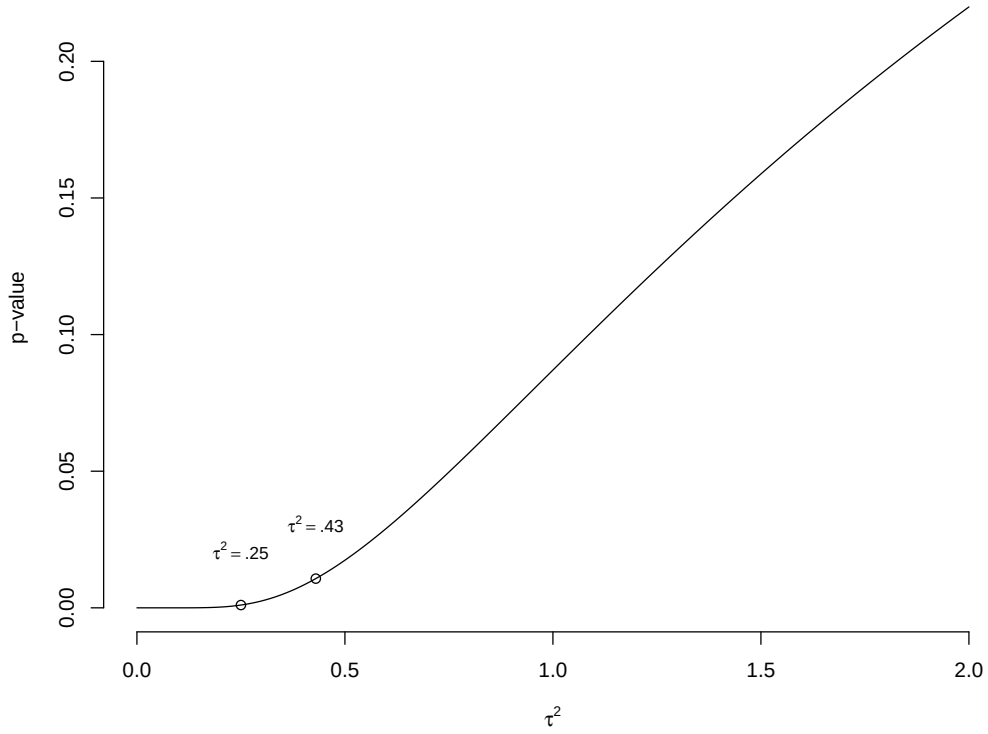

Figure 2: Sensitivity analyses for the p-value that indicates the probability of observing the results from the DECREASE studies, or more extreme results, based on the estimated true effect (non-DECREASE trials) and the accompanying variance estimate.

trials separately and the non-DECREASE trials combined, this resulted in four meta-analytic mortality estimates with corresponding effect variances (see Table 3). Throughout the simulations, we used the point estimates (i.e., fixed effect) to simulate genuine- and fabricated data, but supplemented this by using the more uncertain distribution estimates (i.e., random effects) as sensitivity analyses.

Table 3: Outcome possibilities within a simulated 2 (beta-blocker v control) by 2 (dead v alive) clinical trial.

	Dead	Alive
Beta-blockers	n_{11}	n_{12}
Control	n_{21}	n_{22}

We applied the inversion method to estimate the number of fabricated data points in the DECREASE trials[18]. The inversion method iteratively hypothesizes that X out of N data points were fabricated (i.e., $X = 0, 1, ..., N$). For each combination of X and trial, we simulated 10000 datasets. Each simulated dataset contained X fabricated data points and N-X genuine data points. For each simulated dataset (exact simulation procedure in the next paragraph), we determined the likelihood of the results with

$$L(\theta|\pi_E, \pi_C) = \pi_E^{n_{11}}(1-\pi_E)^{n_{12}} \times \pi_C^{n_{21}}(1-\pi_C)^{n_{22}} \quad (1)$$

where π_E indicates the mortality rate in the beta-blocker condition as drawn from the meta-analytic effect distribution (π_C indicates the mortality rate in the control condition). The likelihood was computed under both the fabricated effect estimates (i.e., $L_{fabricated}$) and the genuine data (i.e., $L_{genuine}$). Table 3 indicates which cell sizes the various n_{XX} refer to within the (simulated) data. After computing the likelihoods, we compared them to determine whether the simulated data were more likely to arise from the genuine trials ($L_{genuine} > L_{fabricated}$) or from the fabricated trials ($L_{fabricated} > L_{genuine}$). Note that comparing the likelihoods is a minor deviation from the preregistration, where we initially planned on using p-value comparisons (osf.io/vnmzc).

For each hypothesis of X out of N fabricated data points, we computed the probability that the fabricated data are more likely than the genuine data ($p_F = P(L_{fabricated} > L_{genuine})$). Based on p_F, we computed the confidence interval for X (i.e., $X_{LB}; X_{UB}$). For a 95% confidence interval, the lowerbound is equal to the p_F closest to .025, whereas the upperbound is equal to the p_F closest to .975.

We computed p_F for all X out of N fabricated datapoints in 10000 randomly generated datasets, which were generated in three steps. For each dataset we:

1. Sampled (across conditions, without replacement) X fictitious participants that would be the result of data fabrication.
2. Determined the population mortality rate for each condition (i.e., for each cell as in Table 3). The meta-analytic point estimate was used or a population effect was randomly drawn from the meta-analytic effect distribution.
3. Simulated the number of deaths for the different conditions using a binomial distribution based on the mortality rate as determined in 2, resulting in the cell counts as in Table 3.

Based on the meta-analytic effect from 2 and the cell sizes from 3, we computed the likelihoods $L_{fabricated}$ and $L_{genuine}$ using Equation 1. As mentioned before, we computed p_F, which indicated the probability that the data are more likely under the estimates resulting from the (allegedly) fabricated data (i.e., the DECREASE trials) than under the estimates resulting from the genuine data (i.e., the non-DECREASE trials; $p_F = P(L_{fabricated} > L_{genuine})$).

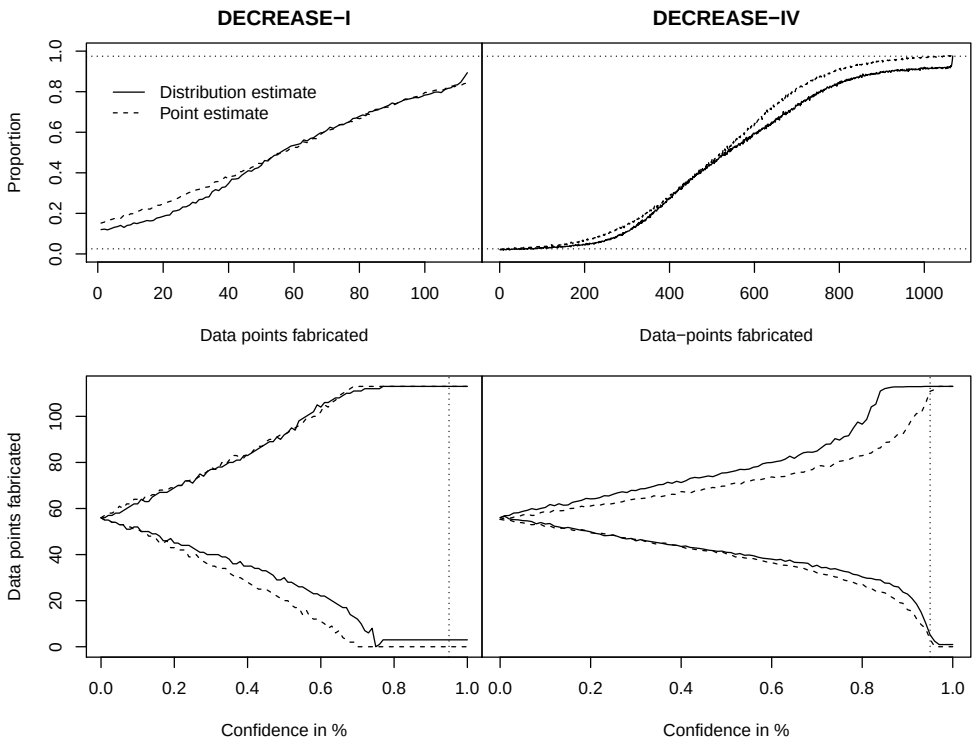

Figure 3: Inversion method results used to estimate the number of data points fabricated in the DECREASE-I and DECREASE-IV trials. The top row panels indicate p_F (y-axis) for all X out of N fabricated data points (x-axis). The bottom row indicates the estimated number of fabricated data points (y-axis) when varying the degree of confidence (x-axis). Dotted lines indicate the bounds for a 95 percent CI.

Results

For DECREASE-I ($N=112), the 95% confidence interval for the estimated number of fabricated data points is [0 - 112] or [2 - 112] when based on a point estimate or a more uncertain distribution estimate, respectively. The left column of Figure 3 depicts the p_F per X fabricated data points (top panel) and the bounds of the confidence interval when the degree of confidence is altered (lower panel). Staying clearly between the dotted lines in the top panel, depicting the 95% CI (top: .975; bottom: .025), it becomes apparent that the degree of uncertainty is too high to make any reasonable estimates about the number of fabricated data points with sufficient confidence. This is partly due to the small sample size of the DECREASE-I trial (i.e., $N = 112$) and the availability of just the summary results. Only when the degree of confidence is lowered to around 75% does the interval not span the entire sample size. As such, based on the summary results, little can be said about the extent of the data fabrication that occurred in the DECREASE-I trial, affirming the conclusions of the original committee report[4].

For DECREASE-IV ($N=1066), the 95% confidence interval for the estimated number of fabricated data points is [0 - 1053] or [8 - 1066] when based on a point estimate or a more uncertain distribution estimate, respectively. The relatively minor difference between the estimates indicates that there is a high degree of confidence that data fabrication did occur based on the difference of the trial results alone. Nonetheless, the range of potentially fabricated data points is still estimated at approximately 1000; this indicates that the summary results are insufficient to provide more than an estimated lowerbound. This indicates that it is possible not all data were fabricated (i.e., $N = 1066$), increasing the importance of well-documented data provenance to discern between genuine and falsified data. This affirms the conclusion of the scientific integrity committee that the results of the DECREASE-IV trial are "scientifically incorrect" (p.11)[3].

The results also highlight that, despite the lack of availability of the raw data, summary results from larger samples allow estimation of the number of fabricated data points when similar trials are available. Moreover, larger trials result in relatively more certainty (e.g., DECREASE-IV) about the estimated number of fabricated data points using the inversion method compared to smaller trials (e.g., DECREASE-I), although much residual uncertainty remains. This increased certainty is due to decreased standard errors at the population level of the estimated effects, resulting in higher sensitivity to data anomalies. Nonetheless, substantially less information is available in just the summary results, and raw data availability would improve results verification and the detection of potential anomalies. These results also highlight that in order to prevent detection, it would be in the fabricators' interest to fabricate small studies even if raw data are hidden away (assuming the fabricator wants to remain undetected).

Discussion

Throughout steps 1, 2, and 3 we provided evidence that the , the DECREASE trials are highly unlikely to come from a genuine data pool, and that there is a high degree of confidence that data was fab

We note that the variance in the non-DECREASE studies was estimated at 0, indicating that there would supposedly be a fixed-effect of beta-blockers on perioperative mortality despite differences in type of beta-blockers administered and dosage/duration of the beta-blockers. This homogeneity is not excessive, considering that the Q-statistic is sufficiently large to begin with (i.e., 5).[19] Nonetheless, the original non-DECREASE trials show substantive variation in the treatment, for example the usage of different beta-blockers (i.e., atenolol, propanolol, bisoprolol, metoprolol) in different (standardized) dosages, which have been argued to affect effectiveness of the interventions[20]. As such, the lack of heterogeneity can be genuine and indicative of no difference between these different beta-blockers and their dosage/duration. Nonetheless, it could also be due to uncertainty in the estimate of heterogeneity τ^2 due to the small set of studies included.

However, due to various types of beta-blockers, evidence might be moderated[20].

Additionally, during the process of this research paper, the first author tried to ascertain a raw dataset of one of the DECREASE trials via a Freedom of Information request (FOI). The Erasmus MC refused to share these data

The ESC/ESA guidelines from 2014[@] were published in October 2014, whereas the meta-analysis indicating a reversal of the effectiveness of beta-blockers was published online at the end of July 2013[@]. The committee revising the ESC/ESA guidelines stated: "The respective writing committees independently performed their literature review and analysis, and then developed their recommendations."[21] Regardless, the revisions made "recommend continuation of beta-blocker therapy in the perioperative period in patients currently receiving this medication" and do not recommend the "initiation of beta-blockers in patients undergoing low-risk surgery"[22]. Review pieces note no substantial clinical change with respect to beta-blockers.[23,24]

The revisions to the ESC/ESA guidelines do not discourage use of beta-blockers, despite the obvious lack of evidence for systematic evidence of the effectiveness of beta-blockers to reduce perioperative mortality in trials. If anything, the trials show that insufficient evidence has been collected. This becomes apparent when the estimated effect for all non-DECREASE trials is inspected; its p-value is .04, which is insufficient evidence and is actually more likely when there is no effect in of beta-blockers in reality[25]

In order , the first author tried to ascertain the data of DECREASE VI, the only DECREASE study for which a dataset is still available[1] via a Freedom of Information (FOI) request. Within this paper, we inspected data anomalies based on summary results, which contain less information to be able to determine what isThe board of Erasmus Medical Centrum (EMC) was unwilling to comply with this request, stating that it was not a matter of the board. Regardless of whether it was a board related matter,

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