Report on the 2012 follow-up investigation of possible breaches of academic integrity

Erasmus MC Follow-up Investigation Committee, 2012

30 September 2012

Contents

Abbreviations

CBS:	Statistics Netherlands (*Centraal Bureau voor de Statistiek*)
CRF:	Case Record Form
Decrease:	Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echo study group
DSE:	Dobutamine Stress Echo
ECG:	Electrocardiogram
Elpado:	Electronic patients' dossier (the name refers to the database as a whole, not to individual patient's dossiers)
METC:	Medical Ethics Committee
MI:	Myocardial infarct
NT-proBNP:	N-terminal prohormone of brain natriuretic peptide
PTA:	Percutaneous Transluminal Angioplasty
SPSS:	Statistical Package for the Social Sciences
WMO:	Medical Research involving Human Subjects Act
ZIS:	Hospital Information System

1. Introduction

1.1. Mandate

On January 1 2012, the Board of Erasmus MC established the investigative committee for academic integrity in order to conduct the follow-up investigation recommended in the report *"Onderzoek naar mogelijke schending van de wetenschappelijke integriteit"* (Investigation of possible breaches of academic integrity), dated November 8, 2011. The working name of this committee is the *Commissie Vervolgonderzoek 2012* (the Follow-up Investigation Committee). It is referred to below as "the Committee."

The Committee membership is as follows:
- Prof. P.J. Koudstal, Professor of Neurology, Erasmus MC
- Prof. B. Löwenberg, Professor of Haematology, Erasmus MC (chairperson)
- Prof. P.J. van der Maas, Emeritus Professor of Public Health , Erasmus MC
- Mr. J.M. Oosting, Head of Legal Affairs, Erasmus MC
- Prof. R.J.G. Peters, Professor of Cardiology, AMC
- Prof. A.J. Rabelink, Professor of Internal Medicine, LUMC

Administrative support has been provided by Dr. R.E. Juttmann, Department of Research Policy, Erasmus MC.

The investigation in 2011 focused on possible breaches of academic integrity in the "Decrease VI" study ("Decrease" standing for the Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echo study group). It also addressed a number of projects that were part of the same line of research as the Decrease VI study. The time that had been allowed for the investigation in 2011 was not sufficient for a full study of all the projects that had been intended for inclusion. The investigation also found indications of other possible breaches of academic integrity, which could not be studied in the time available.

The present Committee is charged with conducting the investigation for which there was insufficient time in 2011. On that basis, the Board has formulated the Committee's task as follows:

"The Committee's task is to investigate whether there were possible breaches of academic integrity in the course of the following research projects, or parts of them:
1. The Decrease IV study
2. The DSE database study, especially with regard to the validity of the reported causes of death
3. The Holter database study
4. The second part of the Decrease II study, which was published as the Decrease V pilot study.
5. Preparatory studies for the Decrease VI studies."

In consultation with the Board, the Committee focused primarily on the scientific soundness of the data in these projects, and on whether it was possible to uphold the findings and conclusions reported in the relevant publications.

The Committee was asked to complete this follow-up investigation before 1 July 2012. The Dean was presented with a draft version on 30 July. In recognition of the right to a fair hearing, the Dean sent this version to two of those who provided testimony, with the request that they express their opinions on it, in a written response. This response reached the Dean on August 12, 2012, and was passed to the committee for evaluation. In light of that response, the committee has modified its draft version in several respects, leading to the present, and definitive, version.

1.2. Working method

In carrying out its mandate, the Committee has drawn on the following sources:

- The research data and report from the Investigative Committee on Academic Integrity dated November 8, 2011.
- Eight witnesses, who were interviewed in part by the entire Committee and in part by groups of members representing the Committee.
- Written answers to a number of questions that were submitted by five of the eight witnesses.
- Written answers by one witness who did not respond to invitations to a personal interview, and was willing only to answer questions in writing.
- Further studies and comparisons of the data that are available in:
    - Case Report Forms (CRFs), patient files and other source documents
    - Research databases
    - The electronic patients' dossier (Elpado) of the Erasmus MC
    - Research reports in the form of publications and theses.
- Support provided by two external research bureaus, Pallas Health Research and Consultancy B.V. and Hoffmann B.V., in relation to the more technical aspects of the investigation.

The findings were discussed during meetings of the Committee at Erasmus MC in Rotterdam and by e-mail correspondence. The Committee met five times.

The conduct of the research projects that were examined, and the publications flowing from these projects, have been evaluated using the description of academic misconduct given in the Research Codes of the Erasmus MC (March 2011). Where the Committee's findings matched this description of misconduct, the Committee has striven in its conclusions to use three terms to describe the shortcomings in a uniform way. These terms are:

<u>Negligent:</u>
The faulty conduct and/or structure of the research means that it is not possible to vouch for the reliability of the results.

<u>Scientifically incorrect:</u>
The use of incorrect methods, such as methods that are not in accordance:

- with accepted standards in scientific practice, or
- with the methodology section of the relevant research protocol and/or the relevant publication.

<u>Based on the use of fictitious data:</u>
Based on the use of data that is objectively incorrect.

Some of the shortcomings that were found can be described with more than one of these terms.

The Committee chose the terms “negligent” and “scientifically incorrect” to specify the example of academic misconduct (“failing to exercise due care when conducting research”) provided in the Research Codes.

At the beginning of its work, the Committee defined the criteria by which a research project could or must be treated as invalid, and which would justify informing the journal in which the relevant study was published. These criteria are:

Criterion 1:	Non-existent people have been included; the data is fictitious.
Criterion 2:	The inclusion and exclusion criteria reported in the publication were not applied consistently, with the result that the patient population actually studied differs in material ways from the published description.
Criterion 3:	Patients have been included without their knowledge; there is no written informed consent (while this is claimed in the publication); when informed consent was requested, patients were incompletely or incorrectly informed.
Criterion 4:	The randomisation was not conducted as reported in the publication; the allocation of subjects to treatment groups was not random.
Criterion 5:	There is no documentation, or only inadequate documentation, of essential research parameters.
Criterion 6:	The conduct of the treatment to which a subject was allocated was insufficiently documented; the treatment has been repeatedly altered without this being reported in the publication; or, in the “intention-to-treat” analysis, patients were not counted in the treatment group to which they were originally allocated.
Criterion 7:	Outcomes are unreliable: there is no definition of outcomes, or the definition is inadequate, or various definitions have been used; there was no independent adjudication committee; or the researchers have influenced or altered the classification of outcomes.
Criterion 8:	There are material differences between the source documentation (the patients’ dossier), the case record form used in the study, the study database, and the publication.

The report will cite these criteria where they are relevant.

2. Reports for each research project

2.1. The Decrease IV study

2.1.1. Introduction

The Committee has evaluated the scientific soundness of the data in the Decrease IV study, and whether the findings and conclusions reported in the study's main publication can be upheld.

The publication in question is

- Dunkelgrun Martin; Boersma Eric; Schouten Olaf; et al.; Bisoprolol and Fluvastatin for the Reduction of Perioperative Cardiac Mortality and Myocardial Infarction in Intermediate-Risk Patients Undergoing Noncardiovascular Surgery A Randomized Controlled Trial (DECREASE-IV); ANNALS OF SURGERY Volume: 249 Issue: 6 Pages: 921-926 Published: June 2009.

Using a Randomized Controlled Trial among patients who had had major non-cardiovascular surgery, the study examined the effectiveness and safety of beta blockers and/or statins in preventing perioperative cardiovascular complications.

2.1.2. Findings

Source documentation

Approximately half of the informed consent forms and the CRFs have been preserved. In other cases, such as ECG results, records of the actual medications used, and records of the basis for the clinical outcome findings, the source documentation was almost entirely lacking. In their statements to the Committee, the authors attributed the lack of source documents partly to the lack of good storage facilities, and partly to the fact that some data was never recorded in source documents, but was instead entered directly as data or its interpretation in the study database. In these cases, these witnesses considered entries in source documents unnecessary, because this was an "unmonitored" study. In some cases, it was not the actual data that was entered in the database, but rather interpretations of this data.

Informed consent

All the witnesses who were asked about the informed consent procedure stated that this was conducted according to protocol. This is supported by the written informed consent forms, although only some of these were available to the Committee.

Inclusion

The research protocol that the researchers submitted to the Medical Ethics Committee (METC), and which the METC approved, set out an inclusion criterion based on a complex point system. The lower limit for inclusion was 40 points and the upper limit 60. According to the witnesses, the points system proved in practice to be too time-consuming. It was replaced by a questionnaire and flow diagram. The Committee examined the patient group in detail and established that, as a result of these changes, patients with a risk level lower than 40 points were also included. The Committee has asked for evidence of the validation of the

questionnaire and flow diagram with regard to the points system, and has not obtained any such evidence. No protocol amendment covering this change was submitted to the METC.

The Committee has established that, as regards the patient selection, the study was not conducted in accordance with the protocol and that this led to the inclusion of patients with a lower risk than was intended in the protocol (< 40 points).

The use of medications

From the statements of witnesses, the Committee has reconstructed the following state of affairs in relation to medication use:

- On the day of inclusion and obtaining informed consent, the patient was randomly allocated to a treatment group on the basis of a system designed by the statistician. The system used envelopes to be opened in a fixed order.
- The prescriptions contained in the envelopes were signed by a PhD candidate (who was also an MD) and given to the patient.
- Each patient who was included was allocated randomly to one of four research groups and was thus eligible to receive one of the four possible medication strategies. The intended medication was recorded in the database indirectly, by recording the randomisation. There was no documentation on the actual use of the study medications, the starting date or the duration of use:
    - Medication use was not recorded in the CRF.
    - When the patient was admitted to the hospital, the PhD candidate asked all the patients whether they had used the prescribed medication. The answers were not recorded.
    - The principal investigator has stated that, as indicated in the publication, the clinical status (especially heart rate) of patients allocated to receive beta-blocker therapy was regularly checked, and that the medication was then adjusted as necessary. These actions are not documented.

In their statements to the Committee, the authors said that they thought records of actual medication use would be of little value, since they proposed to use an “intention to treat analysis.”

Determination of the outcomes

The determination of outcomes was primarily a matter of diagnosing the occurrence of the non-fatal myocardial infarct (MI). The protocol dealt with this as follows:

“The diagnosis *nonfatal MI* requires any two of the following:

1. Characteristic ischaemic symptoms (i.e. chest pain, shortness of breath etc. lasting longer than 20 minutes.
2. ECG changes including acute ST elevation followed by appearance of Q waves or loss of R waves, or new left bundle branch block, or new persistent T-wave inversion for at least 24 hours, or new ST segment depression which persists for at least 25 hours.
3. A positive troponin or peak CK-MB>8% of an elevated total CK with characteristic rise and fall.”

From the statements of witnesses, the Committee has reconstructed the following state of affairs in relation to the determination of outcomes:

- On days 1, 3 and 7 after the operation, laboratory staff took blood samples from all the patients who were included. These were tested for troponin levels, which were recorded in Elpado. The PhD candidate monitored these reports daily. Although the protocol states that an “increase” in troponin should be regarded as a criterion for a myocardial infarct, it did not define the concept of an increase. Any measurable presence of troponin in the blood was regarded as a positive, even once-only low values such as 0.03 mg/l (the lowest value measured in the laboratory).
- In the first week after the surgery, the PhD candidate took an anamnesis from all the included patients, with a focus on confirming or excluding angina pain symptoms. This anamnesis was not recorded in a CRF or any other document.
- On days 1, 3 and 7, a standard 12- channel ECG was made. An extra ECG was made if patients had had angina pain symptoms. As it was not always possible for logistical reasons to perform the ECGs in the usual way (i.e. through the Cardiology Department), most ECGs were performed by the PhD candidate using a mobile ECG machine; they were also evaluated by him. These ECG results were not recorded in Elpado and have not been preserved.
- Patients in whom the PhD candidate found at least one of the three criteria (anamnesis, troponin, ECG), were selected for further evaluation. These patients’ cases were not presented to the “adjudication committee” as specified in the protocol. The protocol states that this committee would consist of one cardiologist, one anaesthesiologist, and one vascular surgeon. In fact the patients selected by the PhD candidate were only presented to the vascular surgeon. This medical specialist was given the following information:
  - a verbal report on the anamnesis
  - the troponin reading
  - a printed ECG.

  On the basis of this information, the vascular surgeon made an individual judgement – without the involvement of the other members of the “adjudication committee” – as to whether there had been a myocardial infarct. The conclusion “myocardial infarct” was drawn if the vascular surgeon considered that at least 2 of the 3 criteria were positive.
- If, in the opinion of the vascular surgeon, there had been a myocardial infarct, this was recorded in the database as an “event.” The justification for this conclusion (i.e. which of the 3 criteria were positive) was not recorded. Due to the lack of anamnesis data and ECG printouts, it is not possible to verify the justifications. In hindsight, some of the authors, who testified to the Committee, saw this lack of documentation as a shortcoming. However, they thought that it was not in conflict with the protocol, since the necessity of this documentation had not been specified in the protocol. Moreover, they argued, it was an unmonitored study.

The Committee has also found that, in a large number of cases, a myocardial infarct which the researchers had recorded could not be confirmed from Elpado and/or the clinical discharge reports.

2.1.3. **The Committee’s conclusions**

Source documentation
The Committee considers the failure to preserve essential source documentation to be negligent [criterion 5]. Researchers have the responsibility and task of ensuring that data from studies which fall under the WMO (Medical Research involving Human Subjects Act), in

which they have a leadership role, is preserved for 15 years. In this case, they used storage facilities whose security and good management were not guaranteed.

The fact that it was not actual data, but interpretations of data, that was stored in this study is, in the eyes of the Committee, negligent. It has made further verification and analysis impossible, both for the researchers and for others who might wish to critically evaluate their work. The fact that this study was not monitored is not, in the Committee's view, relevant in this respect.

Informed consent
The Committee has no demonstrable proof of informed consent for about the half of the participating patients, but assumes on the basis of statements from witnesses that the informed consent procedure was conducted according to the protocol.

Inclusion
The Committee considers that the change made to a rule of inclusion, and the consequent change in the composition of the intended target group for the study, without validation and without permission of the METC, was scientifically incorrect [criterion 2].

Medication use
The Committee views the failure to record actual medication use, in a study focusing on an intervention using medicines, to be questionable [criterion 6]. Even in an "intention to treat" analysis, careful records of the medications used are important to understanding the actual use of the medication that is the subject of the study (is it actually used as prescribed; is it used according to the protocol?). Such records are also important to understanding and interpreting the value of the research findings. However, this is not a question of academic integrity.

Determination of outcomes
The Committee considered the manner in which outcome determination was performed to be scientifically incorrect, because it did not include the independent evaluation of possible perioperative cardiovascular complications (the primary outcome of the research) by an "adjudication committee" consisting of three specialists (the protocol specifies a cardiologist, a surgeon and an anaesthesiologist). The evaluation was performed by only one vascular surgeon. As a result, the expertise of a cardiologist and anaesthesiologist, which was relevant in this study, was structurally lacking, as were discussions between the evaluators [criterion 7].

In general, and particularly in this study, the Committee considers it very important that all the members of an adjudication committee should in fact participate, for the following reasons:

- In most cases, painful symptoms found by the PhD candidate in post-operative patients underlay the conclusion that the patient had, or had not, experienced a cardiovascular complication – in this case a myocardial infarct. The nature and details of these symptoms, and how they were determined, were not recorded, and cannot therefore be checked for accuracy [criterion 7]. In this connection, it is important to note that establishing the existence of anginal pain in patients who have recently undergone major surgery can involve some ambiguities, and demands an adequate level of clinical skills. Given the importance of this finding to the research, the Committee considers it irresponsible that this was left entirely in the hands of a researcher who, as a "junior", had limited clinical experience. The Committee believes that a critical evaluation by an adjudication

committee, leading to the careful documentation of the findings specified in the protocol, was a necessity in this case.
- The interpretation of the protocol with regard to the criterion "positive troponin levels" is problematic, because a once-only very low troponin level, in the context of a post-operative patient, cannot be treated, *ipso facto*, as partial justification for the research outcome "myocardial infarct." When interpreting troponin levels, non-cardiac causes such as a kidney function disorder must be considered. For such interpretations, it is indispensable to work with an expert adjudication committee, as specified in the protocol [criterion 7].

The Committee considered the failure to record and report the justifications for the determinations of outcome – i.e. which of the three criteria were positive – to be negligent [criterion 5]. Good records of outcomes are a scientific necessity. The fact that this study was not monitored is not, in the Committee's view, relevant in this respect.

Perioperative cardiovascular complications are generally so serious that it is very unlikely that a complication would have had no clinical consequences in the patient's treatment regime. It is relevant that the patients generally had no cardiac history, and that, for them, a myocardial infarct would be a new clinical problem. In addition, the Committee must assume that the rationale of the study entailed the evaluation not of sub-clinical phenomena, but of cardiovascular complications that were clinically relevant or had clinical consequences. The frequent lack of reports of perioperative cardiovascular complications in Elpado, and in the clinical letters, is striking, and strengthens the Committee's doubts about the validity of the determination of outcomes [criterion 8].

2.1.4. **The Committee's recommendation**

The Committee considers the conduct of the study at many points to have been negligent and scientifically incorrect. In the Committee's opinion, it is not possible on the basis of the available information to vouch for the reliability of the findings in the publication and the validity of the conclusions. The Committee therefore recommends that the Board of Directors should inform the journal of its findings and conclusions with regard to this publication, and should inform the authors of this in advance.

2.2. DSE database study

2.2.1. **Introduction**

The Committee has investigated the extent to which the contents of the DSE (Dobutamine Stress Echo) database can be regarded as a scientifically sound basis for the results and conclusions of the following publications, which are part of the DSE database study:

- Biagini E, Elhendy A, Bax JJ, Rizzello V, Schinkel AF, van Domburg RT, Kertai MD, Krenning BJ, Bountioukos M, Rapezzi C, Branzi A, Simoons ML, Poldermans D. Seven-year follow-up after dobutamine stress echocardiography: impact of gender on prognosis. J Am Coll Cardiol 2005;45:93-7.

- Feringa HH, Bax JJ, Elhendy A, van Domburg RT, Schouten O, Krenning B, Poldermans D. Hemodynamic responses and long-term follow-up results in patients using chronic beta 1-selective and nonselective beta-blockers during dobutamine stress echocardiography. Coron Art Dis 2006;17:447-53.

The DSE database is a database of clinical data from patients at Erasmus MC who have been assessed with a Dobutamine Stress Echocardiogram (DSE), and for whom various other clinical data has been recorded.

There is doubt about the validity of the causes of death recorded in the database. A witness has stated that, if the cause of death was not explicitly known and the DSE was abnormal, it was assumed that the cause of death was cardiovascular.

Later this witness partially retracted his statement. He explained that this approach was followed during a trial analysis, but he did not know with certainty how the cause of death was determined during the definitive analysis.

2.2.2. **Findings**

According to testimony from the researchers, the reported causes of death were based mainly on written information, which the researchers had requested and obtained from General Practitioners. It appears that this documentation can no longer be found.

The Committee investigated the extent to which the reported causes of death could be validated using records held by the Netherlands Central Bureau of Statistics (CBS). From discussion with the CBS, it was learned that, for privacy reasons, data could be provided only at an aggregated level, so that no individual comparisons would be possible. Therefore, whatever the result of such a comparison might be, it would not be possible to ascertain with certainty whether any differences found were due to possible improper or negligent interpretations made by the researchers.

In the light of this, the Committee could not investigate the matter further.

2.2.3**. The Committee's conclusions and recommendations**

The Committee found that the source documentation in relation to the reported causes of death (the letters from the General Practitioners) is missing. This data provided the foundation for a number of research projects. However, this research was not subject to the Medical Research involving Human Subjects Act and was performed about 10 years ago. The Committee therefore categorizes the lack of the source documentation as unfortunate but not as negligent.

Because of these circumstances, the Committee is not able to investigate the validity of the reported causes of death, or deliver any judgement on the results and conclusions in the publications mentioned above. The Committee makes no recommendations in relation to these studies.

2.3. The Holter database study

2.3.1. **Introduction**

The Committee investigated the extent to which the contents of the Holter database can be regarded as a scientifically sound basis for the results and conclusions of articles that are still to be published in peer-reviewed journals. Thus far, data from the Holter database has been used only in the second chapter of the thesis of Dr. T.A. Winkel:

- TA Winkel. MT Voûte, M de Melis. R Kessels, WJ Flu, JPCM Oomen, JJ Bax, HJM Verhagen, DP Poldermans. Cardiac arrhythmias in vascular surgery patients; is 72-hour continuous monitoring long enough?

The Holter database contains data on patients who have had vascular surgery, and who have been monitored before and after the surgery with a Holter instrument, which is attached to the patient's body externally and gives a continuous ECG record. This database also includes patients who have been monitored before and after the surgery using an implanted heart rhythm monitor (Reveal), for the same purpose. This monitor is implanted under the skin some time before the vascular operation. The aim of the study was to examine whether rhythmic disorders could be detected more accurately with a Reveal than with a Holter. The patients in whom a Reveal was implanted were asked for permission before this implantation and before their participation in the study, and CRFs were completed.

2.3.2**. Findings**

Source documents

From witnesses' statements and other sources, the Committee found:

- Signed informed consent forms and CRFs are available for all the Reveal patients.
- Since the perioperative monitoring of patients with a Holter was standard policy, these patients were not asked for consent. No CRFs were used for the data collected from patients with a Holter. This is observational data which, with the exception of the specific Holter readings, was collected from Elpado (the electronic patients' dossier). The Holter readings were stored on the hard disk of a computer used by the researchers.

Data verification

The Committee selected 20 patients at random from the database, and checked whether the clinical risk factors, type and date of operation, the NT-proBNP level, the troponin level and the research outcome recorded in the database are in accordance with the data in Elpado. The results are as follows:

- For a quarter of the patients who were checked, there were discrepancies, which were generally small, in relation to clinical risk factors. It was found that:
  - the discrepancies in each patient's case related to a single risk factor,
  - risk factors were shown in reverse (for example: where a clinical letter indicated that the patient was currently suffering from angina pectoris and/or that the patient had had a myocardial infarct in the past, the record in the database indicated the converse);
- There are no discrepancies regarding the date and type of operation;
- In two cases, no NT-proBNP level had been recorded in the database, while pre-operation values were available in Elpado.

In addition to these twenty patients, the Committee examined the cases of another five patients with the research outcome “myocardial infarct.” All five discharge reports for these patients contained indications of cardiac ischemia. In some cases, however, these indications were more limited than the definition of a myocardial infarct that was used in the thesis.

2.3.3. **The Committee’s conclusions and recommendations**

The Committee observes that there are some inaccuracies in the Holter database. The study has not yet been published in an international peer-reviewed journal. The Committee advises the researchers to check the data of this study against Elpado or in some other way before proceeding to publication. The Committee advises that the definition of the research outcome should be modified in line with the actual clinical findings, from “myocardial infarct” to another term such as “indications of myocardial ischemia.”

2.4. The Decrease V pilot study

2.4.1. Introduction

The Committee investigated the extent to which the data in the Decrease V study is scientifically sound, and whether the findings and conclusions reported in the main publications from this study can be upheld.

The publications concerned are:

- Poldermans D, Schouten O, Vidakovic R, Bax JJ, Thomson IR, Hoeks SE, Feringa HH, Dunkelgrun M, de Jaegere P, Maat A, et al. A clinical randomized trial to evaluate the safety of a noninvasive approach in high-risk patients undergoing major vascular surgery: the DECREASE-V Pilot Study. J Am Coll Cardiol 2007;49(17):1763–1769

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- Olaf Schouten, MDa, Jan-Peter van Kuijk, MDb, Willem-Jan Flu, MDb, Tamara A. Winkel, MDa, Gijs M.J.M. Welten, MD, PhDa, Eric Boersma, PhDb, Hence J.M. Verhagen, MDa, Jeroen J. Bax, MDd, and Don Poldermans, MDc. Long-Term Outcome of Prophylactic Coronary Revascularization in Cardiac High-Risk Patients Undergoing Major Vascular Surgery (from the Randomized DECREASE-V Pilot Study) : Am J Cardiol. 2009 Apr 1;103(7):897-901.]

The study was part of the Decrease II study, which had the following two objectives:

Objective 1:
To determine the added value of a dobutamine stress echocardiogram (DSE) or a nuclear myocardial perfusion scan in preventing perioperative cardiovascular complications in vascular surgery patients who have one or two risk factors for complications and are being treated with beta blockers (**patient category 1**).

For this objective, such patients were randomly allocated to using, or not using, a DSE or nuclear scan (one of the two, depending on availability).

Patients with more than two risk factors all received a DSE or nuclear scan (**patient category 2**).

Objective 2:
To evaluate the effect of coronary revascularisation on perioperative cardiovascular complications in patients without angina pectoris or with stable angina pectoris, and with extensive myocardial ischemia as shown by means of a DSE or a nuclear myocardial perfusion scan.

For this objective, such patients were randomly allocated to receive, or not receive, preventive coronary revascularisation. According to the research protocol, these were patients with seriously abnormal readings from a DSE or nuclear scan, from both of the above-mentioned categories.

The study structured around the second objective was published as the Decrease V pilot study. Since the statistical power that had originally been intended was not achieved for objective 2, the results regarding this objective were published as a pilot study.

2.4.2. **Findings**

In their testimony as witnesses, the principal investigator and the other researchers involved have stated that the study for objective 2 was part of the Decrease II study, and that the informed consent procedure, data collection and determination of outcomes was performed in accordance with that protocol.

In line with the findings regarding the Decrease II study, set out in the report of the Investigative Committee on Academic Integrity, dated 8 November 2011, the Committee therefore finds as follows:

Informed Consent
- Two witnesses, including, at first, the principal investigator, state that only verbal informed consent was sought. Most of the CRFs have a tick beside “oral informed consent,” and not beside the option “written informed consent.” This approach conflicts with the protocol [criterion 3]. In fact, the option “oral informed consent” should not even have appeared on the CRFs, because the protocol only allowed for inclusion on the basis of written informed consent.
- Two other witnesses stated that written informed consent was requested.
- The Committee has not found any signed informed consent forms.

Data collection
- It is estimated that less than half the CRFs for the Decrease II study have been preserved. No CRFs have been found for the Decrease V study.
- Although one researcher reported that the CRF was, as usual, the standard document for data collection, the principal investigator stated that CRFs should be regarded more as work notes. It was said that loose notes, which are no longer available, were also used. This claim is incompatible with the statement of one researcher, who claimed that the CRF was the primary document.
- Comparison based on a limited random sample of source documents from the Decrease II study, Elpado and the study database produced a considerable number of discrepancies. In the Decrease V study, the key linking the patients included in the research data and

patients' identification numbers in the Hospital Information System (HIS) is no longer available, meaning that no direct comparison could be made for this study. On the basis of witnesses' statements that the same methodology was used in the Decrease II and Decrease V studies, the Committee must assume that these discrepancies are also likely to have occurred in the Decrease V study.
- It is important to note the discrepancies between source documents (including written patient information from other hospitals, doctors, etc.) and the conclusions drawn from them in this study with respect to a patient's risk profile (an essential element in the study) [Criterion 8]. The principal investigator explained that the risk profile was in principle verified by the anamnesis; he claimed that written data was taken into account where it was available. He argued that this approach was in accordance with the guidelines that were valid at that time. This explanation is not comprehensible for the Committee: some factors in the risk profile can be determined only from test results, such as a pathologic Q-wave on the ECG, or a creatinine level of more than 160 micromol/l. While this may possibly partly explain the discrepancies that were found, it does not justify them.
- According to the principal investigator, the DSEs (Dobutamine Stress Echocardiographs) were evaluated by a forum of five doctors using video images. The outcome was determined by majority vote, and was entered into the research database soon afterwards. This outcome is not reported in the CRF [criterion 5]. However, as in many cases the results from another test were entered in the database by a researcher, the CRF outcome does not always match the outcome in the database, and does not always correspond to the data recorded in the context of patient care [criterion 8]. No reports of the evaluation procedure were made, and the original video tapes have been lost. The working method described here therefore differs markedly from the research protocol that had been approved by the METC.

Determination of outcomes
The way the clinical outcomes and study outcomes were determined in practice differed from the protocol and the published reports. The independent determination by two cardiologists and others stipulated in the protocol and by the "adverse-events committee" reported in the publication never existed [criterion 7].

2.4.3. **The Committee's conclusions**

The Committees conclusions regarding the Decrease V study are again consistent with those regarding the Decrease II study, which were stated in the report of the Investigative Committee on Academic Integrity, dated 8 November 2011:

Informed Consent
The Committee finds that the informed consent procedure was applied negligently. This conduct is contrary not only to the national and international guidelines, but also to legislation and regulations relating to clinical scientific research [criterion 3].

Data collection
The Committee considers the failure to preserve CRFs to be negligent. For the Committee's remarks regarding the preservation of source documents, see also section 2.1.3 of this report.

On all the other points that have been referred to, the Committee considers the way in which data collection was done to be both negligent and scientifically incorrect [criteria 5 and 8]. The Committee considers the deliberate deviation from the described method of determining the risk profile of each patient to be scientifically incorrect [criterion 2].

Determination of outcomes
The Committee considers as scientifically incorrect the way in which the outcomes were determined [criterion 7]. Since, in the Decrease V study, the randomisation to a cardiovascular intervention was also based on the outcome determination, it is possible that the negligent and incorrect manner of data collection also had consequences for the patients' clinical treatment. The Committee has not found any evidence of such consequences, and finds that it is impossible to investigate in retrospect whether this has actually occurred. Individual patients can no longer be identified. Due to the lack of source documentation, it is not possible to ascertain whether, as a result of the negligent and incorrect manner of data collection, some patients were incorrectly subjected to a cardiovascular intervention, and whether they suffered as a result.

2.4.4. The Committee's recommendation

The Committee considers that the conclusions of the report *Onderzoek naar mogelijke schending van de wetenschappelijke integriteit"* (Investigation of possible breaches of academic integrity) (November 8, 2011) in relation to the Decrease II study also apply to the Decrease V study. On the basis of the available information, the Committee considers that it is also not possible, in relation to the Decrease V study, to vouch for the reliability of the findings in the publications and for the validity of the conclusions. The Committee recommends that the Board of Directors should inform the journal of the Committee's findings and conclusions with regard to the publications, and should inform the authors of this in advance.

2.5. The Pilot Studies for Decrease VI

2.5.1. Introduction

The Committee has investigated the extent to which the following publications can be regarded as scientifically sound, and whether it is possible to uphold their results and conclusions:

1. Feringa HH, Elhendy A, Bax JJ, Boersma E, de Jonge R, Schouten O, Karagiannis SE, Schinkel AF, Lindemans J, Poldermans D; Baseline plasma N-terminal pro-B-type natriuretic peptide is associated with the extent of stress-induced myocardial ischemia during dobutamine stress echocardiography; Coronary Artery Disease 2006, 17: 255-259

2. Feringa HH, Bax JJ, Elhendy A, de Jonge R, Lindemans J, Schouten O, van den Meiracker AH, Boersma E, Schinkel AF, Kertai MD, van Sambeek MR, Poldermans D; Association of plasma N-terminal pro-B-type natriuretic peptide with postoperative

cardiac events in patients undergoing surgery for abdominal aortic aneurysm or leg bypass; Am J Cardiol. 2006 Jul 1;98(1):111-5. Epub 2006 May 6

The research described in these publications focuses on the extent to which pre-operative NT-proBNP levels measured in the blood of patients facing a major vascular operation is a predictor for:
- the findings from Dobutamine Stress Echography (DSE), and
- the development of perioperative cardiovascular complications.

This research question is very similar to that of the Decrease VI study.

2.5.2. Findings

Database

The Committee had access to a database in the form of an Excel file which it labelled "Database D". Database D had been provided to the Committee by a witness who stated that in mid-March 2007 the first author had put this database on a USB stick in his presence, and had given it to him. According to this witness, this was done on the instructions of the principal investigator (the last author), with the intention that this data should be available for the Decrease VI study. On 26 March 2007, he (i.e. the witness) sent this file by email to a fellow researcher for his or her information. The Committee has this e-mail, from which it appears that Database D already existed on 26 March 2007, in the form that it was presented to the Committee. Database D was created on 10 January 2005.

The Committee first examined to what extent Database D could be regarded as relevant to an evaluation of the data reported in the publications. The Committee therefore compared Database D in detail with the two publications. In addition, a statistician not linked with Erasmus MC repeated and compared the analyses of the two publications on the basis of Database D. Taking into account the fact that one patient appears to be missing in the database, the database and the two publications are in accord in almost all respects with regard to patient characteristics and outcomes. The essence of both publications can be fully reconstructed on the basis of Database D.

The Committee then compared Database D with data from the Erasmus MC's electronic patients' dossier (Elpado). In addition, the Database D data for DSE results was compared with the "DSE database," a file in which DSE results and other data were, at the time of these studies, recorded (see also section 2.2). It is not standard procedure to record DSE results in Elpado.

Database D contains 169 patients. Eight patients are entered in the database twice, and 3 patients are entered three times. There are therefore 155 unique patients. In the cases of 8 patients, no access to Elpado was obtained. The findings with regard to the 147 other patients are as follows:

Patients:

On the basis of the Hospital Information System patient numbers (ZIS numbers) that are included in the database, it was established that all 147 patients are known to Erasmus MC. Only 5 patients in all complied with the inclusion criteria, of having had an operation, a DSE,

and an NT-proBNP measurement within the inclusion period. Even if it is supposed that the NT-proBNP measurements were not included in Elpado, but were recorded on a separate list, there are still no more than 5 patients who both underwent the correct surgery and had a DSE during the inclusion period.

Surgery:

According to the publication, all the patients were operated on for an aneurysm of the aorta abdominalis, or received bypass surgery in the leg. But according to the database, four patients had other surgery instead: a knee operation, traumatic wound surgery, and, in two cases, a neurosurgical operation. Only the traumatic wound surgery is reported in Elpado in accordance with the database.

As for the patients who, according to Database D, underwent surgery for an aneurysm of the aorta abdominalis or bypass surgery in the leg:

- 19 (13 %) were operated on in accordance with their entry in the database. However, only 7 (5 %) of these operations actually occurred within the inclusion period stated in publication 2.
- 20 (14%) of the patients were operated on in accordance with their entry in the database, but the date of the operation does not match the date in the database. Three operations occurred within the inclusion period, while the remaining 17 operations took place outside the inclusion period of publication 2.
- 50 (35 %) of the patients were never operated on at Erasmus MC.
- On the date stated in the database, 15 (11 %) of the patients underwent an intervention that was different to that reported in the database. These operations were a tracheotomy, a large bowel resection, the removal of a blockage in a carotid artery, a Percutaneous Transluminal Angioplasty (PTA) procedure with the insertion of a stent in the right internal carotid artery; a varicose vein operation on the right leg; the surgical treatment of tendovaginitis; Fegan's compression sclerotherapy for varicose veins; the repair of a Cimino fistula; a muscle biopsy; removal of a toenail matrix, and a laryngoscopy.
- 39 (27 %) of the patients received their surgery on a day different to that reported in the database. These operations were surgical interventions of a completely different nature, including a coronary artery bypass; the removal of a blockage in a carotid artery; eye operations; orthopaedic operations; dialysis shunts; a fasciectomy on the hand with a Wolfe graft; correction of an inguinal hernia with mesh; excision for hidradenitis; a triple endoscopy; laryngoscopy; hemithyroidectomy without sternotomy; urological operations; mediastinoscopy, insertion of a peripheral drip; and a spinal operation.

According to the database, 12 patients received surgery on January 1, 2005. This was incorrect in all cases.

NT-proBNP

- For 68 (46 %) of the patients, the result in the database matches that in Elpado. Sixty-six of these measurements were taken within the inclusion period of publications 1 and 2.
- In 22 (15 %) of the patients, the measured values match, but the date does not (ranging from typing mistakes to large discrepancies). Twenty-one of these measurements were taken within the inclusion period of publications 1 and 2.
- In 1 (1 %) patient, the date matches, but the measured value is from another date.

- In 1 (1 %) patient, the recorded date does not match with the measured value, but a measurement was taken on that day. However, the value that was recorded was measured on another day.
- In 45 (31 %) of the patients, no NT-proBNP results at all were found in Elpado.
- In 10 (7 %) of the patients, while NT-proBNP results were included in Elpado, both the level and the date of measurement in Elpado differed from the data in the database.

Dobutamine Stress Echography (DSE) results
In the case of the DSE database, in which the results of Dobutamine Stress Echographs were recorded separately, patients have been traced by surname rather than by their ZIS number (the unique code used to identify patients individually in the hospital information system). Once the surname has been found, the ZIS number can be checked in the DSE database. By this route it was possible to trace patients for whom no access was obtained in Elpado. However, in three cases it was not possible to say with certainty whether the patient did appear in the DSE database. The DSE database contained no data in relation to the type and date of operations and NT-proBNP measurements.

The findings with regard to the 152 verified patients are as follows:
- 89 (59 %) of the patients could be found in the DSE database. This includes five patients for whom no access to Elpado had been obtained. However only 23 of these DSEs occurred within the inclusion period of publication 1.
- 5 (3 %) of the patients underwent a nuclear scan rather than a DSE; two of these were performed within the inclusion period. It should be noted that nuclear scans are not included in the publication.
- 58 (38 %) of the patients could not be found in the DSE database.

A comparison of 12 of the DSE results in the DSE database with information in Database D found discrepancies in more than half of the patients.

Statements from the researchers
The principal investigator:
The principal investigator appeared as a witness before the Committee and stated that:
- The basis for the research was a list of patients with associated NT-proBNP results provided by staff at the Clinical Chemistry Laboratory. (This statement was supported by three other authors, who testified to the Committee.)
- He did not know to what extent these results were also recorded in Elpado. Since these results were from a measurement method that was still experimental, he does not exclude the possibility that, for that reason, they have still not been entered in Elpado for some patients.
- The PhD candidate (the first author) used Elpado to investigate which patients had serious vascular complaints and had undergone one of the serious vascular operations mentioned in the publications.
- The PhD candidate collected the other supplementary data from Elpado and other sources (in particular, the DSE result was not always reported in Elpado, but was recorded in a separate database).
- The principal investigator checked the work of the PhD candidate at random and never noticed anything unusual. He never specifically checked in Elpado whether the operations patients had received matched the inclusion criteria.

- The principal investigator cannot remember giving any instructions to transfer the database from these studies to the witness referred to above. He considers that such an instruction would be illogical, because this witness had nothing to do with these studies.
- The principal investigator had no explanation for the great discrepancies between the Excel file that apparently goes with these publications and the data in Elpado. He put forward the possibility that the file may have been altered later.
- The principal investigator cannot provide the original database on which the publications were based. During his time as a researcher at Erasmus MC, he, together with his PhD candidates and fellow researchers, used and worked on various databases containing data from research patients, including these 170 patients. This was a dynamic activity. No copy of the database was "frozen" and stored for each publication produced. The first author expanded the database containing 170 patients such that it eventually contained 306 patients, on whom a publication was written. After that, this database was no longer used. It was reported to have remained under the control of the first author and never to have been transferred to the principal investigator.

The first author:
In view of its findings, the Committee desired very much to interview the first author-researcher (who lives in the US) regarding the conduct of the study, and made repeated attempts to this end over a period of 2 months. Despite emphatic requests, the offer of flexible arrangement for an interview to fit in with the author's diary, and an offer to reimburse all costs, this author has not agreed to the request to respond to the Committee in person, by telephone or in a video conference. He was prepared only to answer questions in writing, and presented the following statements:
- All the data that the first author used to compile the database on which the publications were based derived from databases provided to him by the principal investigator and (with regard to some of the NT-proBNP levels) by staff of the Clinical Chemistry Laboratory. He did not draw data from Elpado.
- The first author never had occasion to doubt the integrity of the data supplied by the principal investigator, and did not check it against Elpado.
- The first author has no explanation for the substantial agreements as regards analysis and results between Database D and the publications, nor for the considerable discrepancies between the patient information in Database D and Elpado.
- The first author assumes that Database D cannot be the original study database, because that was an SPSS file rather than an Excel file. In addition, the analyses do not match exactly: there were 170 patients rather than 169.
- The first author states that he did not give the relevant database to the witness referred to above in March 2007.
- On the basis of databases provided by the principal investigator, the database with 170 patients was expanded to ultimately include 306 patients, on the basis of which a publication was written. At the time of the first author's departure, in 2008, he left all these databases behind on a computer which was in the care of the principal investigator. (The Committee has not been able to trace this computer further).

Head of the Department of Clinical Chemistry
The Head of the Department of Clinical Chemistry enquired within his Department about events relating to the writing of the publications named above. No one in the Department can remember there having been a list of patients with NT-proBNP levels that was provided to the authors. They considered the existence of such a list, outside Elpado, to be improbable, but could not state this with certainty. According to the Clinical Chemistry Laboratory, all

clinical NT-proBNP results for each patient should be in Elpado. The only exception to this would be results for blood samples that were collected and preserved for other than clinical purposes, for example for research objectives.

Discrepancies between the authors' statements and the publications
On the basis of the interviews with the principal investigator and two other authors, and also of the statements of the first author, it appears that the NT-proBNP results provided the starting-point for establishing the study database. Starting with these results, the possibility of linking the DSE database to the ZIS numbers (the unique patient codes in the hospital information system) was examined. The operations were then searched for in Elpado, or derived from another database.

In contrast to the above, publication 1 states that these were "consecutive patients" who were known to have cardiovascular disease, or were suspected of having it, and who were referred to Erasmus MC for a DSE between October 2003 and December 2004. Similarly, publication 2 states that these were "consecutive patients" who would undergo a major vascular operation in Erasmus MC between October 2003 and December 2004, and who were included prospectively after obtaining consent.

Both publications report that the Medical Ethics Committee (METC) approved the protocol. This is not the case. Moreover, both publications state that interviews or structured interviews were conducted with the included patients and that hospital files were used. Publication 2 states that all patients were included after giving informed consent. The Committee's interviews with the researchers produced no indications that these interviews with patients took place.

2.5.3. The Committee's conclusions

General conclusions

1. The actual existence of Database D is undeniable.
2. Database D consisted largely of factually incorrect data [criterion 8].
3. The essential contents of two publications can be fully reconstructed on the basis of Database D.
4. The Committee considers that the last two points allow for only two explanations:
    A. Database D was created in the course of the relevant academic processes with the purpose of producing the relevant publications, by analysing the data, *or*
    B. Database D was fabricated retrospectively, on the basis of publications that already existed, with the malicious intent of discrediting these publications.

5. The Committee considers explanation B unlikely. In the first place, retrospective reconstruction based on existing publications is practically and technically very complex, if not entirely impractical. In the second place, in the light of the provenance of the database, the reconstruction would have to be attributed to the witness who supplied this database to the Committee. Technical and forensic ICT examination by Hoffmann BV had demonstrated that the Excel file concerned was first generated on 10 January, 2005. At that time, the witness concerned had no relationship at all to the research group. On 26 March 2007 the witness sent the database, in the form in which the Committee now has it, to a colleague as an email attachment. The Committee has

this email. At the time, the witness had been part of the research group for only a few weeks. The Committee considers it unthinkable that, within the time available, this witness should have had any occasion to initiate such a malicious misrepresentation; it also considers that it would not be possible, in view of the complexity of the database, for the witness to have compiled the database with all its details in such a short period.

6. The Committee is therefore convinced that explanation A is the correct one, and that fictitious data has been used, which is a serious breach of academic integrity [criteria 7 and 8]. This conclusion is reinforced by the facts that, despite repeated requests, the researchers have not been able to produce any other database, and that Database D was generated in the period when the publications were being prepared.

7. The Committee is unable to say anything about who should be considered responsible for the production of the fictitious data, as the first author and the principal investigator have produced contradictory statements regarding the way in which the data was produced. Each says that the other was responsible. Moreover, both say that they never checked the research data against patient information.

8. Given the discrepancies between the authors' statements and the text of the publications (see 'Discrepancies between the authors' statements and the publications,' in section 2.5.2 above), the Committee considers the reporting of the research to have been negligent and scientifically incorrect [criteria 2 and 8].

Conclusions in relation to the first author

In view of its conviction that fictitious data has been used, the Committee considers that the first author of the above publications fell short in implementing these studies. The first author was responsible for the use of the data that constituted the basis of the analyses, and then of the findings and conclusions. He performed the analyses himself, on a database which he alone controlled. He had access to the patient information in the hospital information system and Elpado; the database with which he worked consisted, in the Committee's view, largely of patient information which was entirely inconsistent with these sources. The Committee cannot trace the origin of the multiple errors, but considers that, in any case, these should not have escaped the attention of the first author. As reported above, the Committee considers that this was work based on fictitious data, and considers this a serious case of academic misconduct.

The Committee found the lack of an interview with the first author a serious impediment. Because this witness consistently declined repeated invitations for an interview with the Committee, the Committee had no opportunity to enter into an open dialogue with him. Experience has shown that, with regard to some parts of the investigation, the written exchange of question and answer produces an insufficiently clear picture. Written responses to questions cannot be considered equivalent to an interview in which, while hearing both sides of the question, the Committee can interact directly with the witness and ask follow-up questions, and can give the witness an opportunity to provide a detailed explanation.

2.5.4. The Committee’s recommendations

The Committee recommends that the Board of Directors should inform the journals concerned of its findings and conclusions with regard to the publications mentioned above, and should inform the authors of this in advance.

3. Conclusions and recommendations

3.1 The studies

The conclusions and recommendations for the five studies or study sections that were investigated are summarised in the table below:

Project	Conclusion	Recommendation
Decrease IV study	The conduct of the study was in several respects negligent and scientifically incorrect [criteria 2, 5, 6, 7 and 8].	Inform the journal and inform the authors in advance.
DSE database	Essential source documents are lacking in research that did not fall under the WMO. This makes it impossible to validate the reported causes of death. This did not involve a breach of academic integrity.	No recommendations.
Holter database	No serious irregularities were found.	Do not proceed to publication without supplementary checks of data quality.
Decrease V pilot study	The conclusions regarding the Decrease II study in the report dated 8 November 2011 also apply to the Decrease V study. The conduct of the study was negligent and scientifically incorrect [criteria 2, 3, 5, 6, 7 and 8] on a number of points.	Inform the journals and inform the authors in advance.
Pilot Studies for Decrease VI	It is the Committee's view that the study was based on fictitious data [criteria 7 and 8]. The reporting of the study was in some respects negligent and scientifically incorrect [criterion 8].	Inform the journals and inform the authors in advance.

3.2. Consequences for PhD theses

In line with its mandate, the Committee has focused on whether the conclusions of the research projects that were investigated can be upheld in the form in which they were reported in the relevant publications. The recommendations are therefore limited to this topic. Since all the publications were also parts of various PhD theses, the Committee also considered whether its findings have implications for the theses. With regard to these theses, the Committee has decided not to make any recommendations. The factors that have weighed with the Committee are:

- The academic community can be adequately informed about the shortcomings of the studies by writing to the journals in which the studies were published.
- A thesis is intended as evidence of academic competence. This is demonstrated by the thesis as a whole. The Committee does not wish to disqualify theses on the basis of the few chapters that the Committee has examined.
- In so far as PhD candidates may have been involved in academic misconduct in any form, the Committee takes into account that they were in a dependent, and therefore vulnerable, position in relation to the principal investigator. While the Committee considers that PhD candidates do bear responsibility with regard to the academic integrity of their own research, it has the general impression that the candidates in question had too little overview and opportunity to question the principal investigator's working methods.

3.3. General conclusion and recommendation

The report of the investigative committee on academic integrity dated 8 November 2011 has done considerable harm to the reputation of the research group involved. This 2012 follow-up investigation has not been able to limit this harm.

A considerable volume of academic work was performed in this research group. In deciding whether or not to initiate further investigation of this work, it will be necessary to ask whether the importance of this investigation to science and society would outweigh the effort and cost entailed. In view of failures in record-keeping in the various projects, it would also be necessary to consider the limited practical feasibility of such investigation, whose practical feasibility is also limited by the contradictory statements made by the researchers on many points. The Committee considers that further investigation of this work would be indicated only if compelling new scientific or social arguments arise in relation to specific components of it.