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FACULTY OF MEDICINE AND LIFE SCIENCES

Master of Biomedical Sciences

Master's thesis

The NOMICS study: The neurological outcome after minimal invasive Endoscopic coronary artery bypass grafting (Endo-CABG)

Supervisor :
dr. Ingrid ARIJS

Supervisor :
Dr. BJÖRN STESSEL

Fidel Vaqueriza

Thesis presented in fulfillment of the requirements for the degree of Master of Biomedical Sciences

universiteit hasselt | Maastricht University

Transnational University Limburg is a unique collaboration of two universities in two countries: the University of Hasselt and Maastricht University.

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KNOWLEDGE IN ACTION

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Fidel Vaqueriza, 1131031

2nd Master biomedical sciences – Clinical molecular sciences

Senior practical training, November 2016 – June 2017

Jessa Hospital, Hasselt, Belgium

External Promoter: Dr. B. Stessel

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LIST OF ABBREVIATIONS

ACT	Activated Clotting Time
ALT	Alanine Amino Transferase
AST	Aspartate Amino Transferase
BMI	Body Mass Index
CABG	Coronary Artery Bypass Grafting
CAM-ICU	Confusion Assessment Method for the Intensive Care Unit
CES-D	Center for Epidemiological Studies Depression scale
CPB	Cardio Pulmonary Bypass
CT	Computed Tomography
CVA	Cerebrovascular Accident
Endo-CABG	Endoscopic Coronary Artery Bypass Grafting
EQ-5D	EuroQol Five Dimensions
ICU	Intensive Care Unit
MICS	Minimal Invasive Cardiac surgery
MiECC	Minimal Invasive Extracorporeal Circulation
MMSE	Mini Mental State Examination
MRI	Magnetic Resonance Imaging
NOMICS	Neurological Outcome after Minimal Invasive Cardiac Surgery
PCI	Percutaneous Coronary Intervention
POCD	Postoperative Cognitive Dysfunction
QOL	Quality Of Life
RAP	Retrograde Arterial Perfusion
RAVLT	Rey Auditory Verbal Learning Test
RCI	Reliable Change Index
SFQ	Surgical Fear Questionnaire
SGPT	Serum Glutamic-Pyruvic Transaminase
SGOT	Serum Glutamic Oxaloacetic Transaminase
STD	Standard Deviation
TEE	Transesophageal Echocardiography
WAIS	Wechsler Adult Intelligence Scale

ABSTRACT

Despite major improvements in cardiac surgery methods and care the past few decades, neurological conditions after cardiac surgery remain a recurrent problem. At the Jessa Hospital, Hasselt, a new minimal invasive procedure of coronary artery bypass grafting (CABG) has been introduced.

Minimal invasive Endoscopic-coronary artery bypass grafting (Endo-CABG) has proven to reduce hospitalization costs, increase postoperative quality of life, and reduce mortality compared to the conventional CABG method. Only, the neurological outcome after Endo-CABG surgery has not been studied extensively over the years. In this study we tried to assess the incidence of postoperative neurological complications. Mainly stroke, delirium and postoperative cognitive dysfunction were studied, because these are the most common neurological complications after cardiac surgery. We want to compare these incidences with the incidences seen in the conventional CABG surgery studies about the neurological outcome.

In the recent study three groups were included (Endo-CABG, Percutaneous coronary intervention (PCI), and healthy volunteers). These groups were neurologically tested at a baseline moment and a follow-up moment three months after cardiac surgery or after baseline assessment. Also stroke and delirium were tested postoperatively. We compared the postoperative incidence of the neurological complications after Endo-CABG surgery to incidences of conventional CABG surgery.

No significant differences could be found because only preliminary data could be used, but there is a major indication that the neurological outcome after Endo-CABG tends to be similar to that of PCI interventions more than it is related to conventional neurological outcome after conventional CABG. But still neurological complications show to be recurrent after cardiac interventions.

ABSTRACT (NEDERLANDS)

Ondanks grote vooruitgang op vlak van cardiale chrirugie en postoperatieve zorg, blijven neurlogische complicaties vak voorkomend na cardiale chirurgie. In het Jessa ziekenhuis, Hasselt, werd er een nieuweminimaal invasieve methode geïntroduceerd voorhet uitvoeren van coronaire arterie bypass grafting (CABG) operaties.

Minimaal invasieve endoscopische coronaire arterie bypass grafting (Endo-CABG) heeft bewezen dat het in vergelijking met de conventionale CABG een verlaagde hospitalisatie kost, een verhoogde kwaliteit van leven en een verlaagde mortaliteit met zich meebrengt. Alleen is er nog maar weinig geweten over de neurologische uitkomst na Endo-CABG operaties. In deze studie zat getracht worden om de incidentie van neurologische complicaties na Endo-CABG operaties te bestuderen. Vooral beroerte, delirium en postoperative cognitieve dysfunctie (POCD) zullen bestudeerd worden, aangezien deze de meest voorkomende postoperatieve neurologische complicaties zijn. Deze incidenties willen we dan gaan vergelijken met de die we zien bij de conventionele CABG methode.

In deze studie werden 3 groepen geïncludeerd (Endo-CABG, percutane coronaire interventies (PCI), en gezonde vrijwilligers). Deze groepen werden neurologisch gestest op zowel een baseline moment als op een follow-upmoment 3 maanden na de operatie of na de baseline meting. Ook beroerte en delirium werden postoperatief gemeten. We vergelijkten de postoperatieve incidnentie van neurologische complicaties na End-CABG operaties met deze incidenties na conventionele CABG operaties.

Er konden geen significante verschillen gevonden worden tussen deze twee groepen. Dit omdat we enkel preliminaire data konden gebruiken van deze studie. Maar er kon wel een grote indicatie gegeven worden dat de data van de Endo-CABG groep meer overeenkwam met de data van de PCI groep dan met de incidenties die bij de conventionele CABG operaties gezien worden. Ondanks deze verlaging in neurologische complicaties na Endo-CABG operaties blijft de neurologische uitkomst na cardiale chirurgie een wederkerend probleem.

1. INTRODUCTION

Coronary artery bypass grafting (CABG) surgery has a central role in the treatment of patients with ischemic heart disease (1). Despite improvements in both surgical and anaesthetic techniques, Cardiac surgery remains associated with postoperative neurological disorders (2, 3).

The American College of Cardiology and the American Heart Association have classified the different neurological complications after cardiac surgery into two categories, namely type I and type II (4). Type-I neurological disorders include stroke and transient ischaemic, coma and fatal cerebral injury. These disorders have clearly defined diagnosis methods and can be diagnosed performing a clinical neurological examination. In contrast, type-II neurological disorders are far more diffuse and are not well-defined. Type-II neurological disorders include delirium and postoperative cognitive dysfunction (POCD). These disorders involve deficits of memory, concentration and psychomotor speed (5). Together the different neurological deficits expressed after cardiac surgery have a negative effect on the quality of life, healthcare costs, duration of hospitalisation, and the mortality (6-8).

1.1 STROKE

For the conventional CABG method, incidences of neurological complications after surgery have been unchanged for the last decades. The incidences of cerebrovascular accident (CVA) or stroke after conventional CABG procedures range between 1.6 to 5%, depending on patient populations and individual surgical procedures (5, 9-11).

Traditionally, the mechanism of CVA occurring during cardiac surgery is that of macroembolisation or microembolisation (12). Recent data, however, suggest that the systemic inflammatory response and hypoperfusion may also be sources of neurologic injury (13). In a lot of cases neurologic injury is caused by multiple factors. Caplan and Hennerici showed an example of this by stating that the combination of both hypoperfusion and microembolisation increase the risk of neurologic injury (14), this owing to a decreased washout of emboli. The risk of CVA is the highest in the first days after surgery and is easy to diagnose (15). When there is an indication of stroke, a CT or MRI scan of the brain will be made to diagnose CVA if present.

1.2 DELIRIUM

Delirium is defined as an acute disturbance in attention. This occurs over a short period of time and is accompanied by an acute decline in cognition (16). Initially, it was thought that delirium was part of critical

illness, and was not identified as an independent condition. But more and more evidence point out that delirium is a more significant problem than first was thought (17). Delirium is associated with longer hospital and intensive care unit (ICU) length of stay, long-term cognitive dysfunction and even higher mortality rates (18-21).

The incidence of delirium after cardiac surgery can be up to 30% and can be even higher in critically ill patients (18, 22). Postoperative symptoms of delirium are seen in the first one to 3 days after surgery. There are different subtypes of delirium: hyperactive, hypoactive and mixed-type (23). Hyperactive delirium is characterised by different symptoms: increased restlessness, anxiousness, agitation and combativeness. Hypoactive delirium is characterised by drowsiness, sedation, somnolence, or lethargy. Mixed type delirium patients have symptoms resembling both hypo- and hyperactive delirium symptoms. Hyperactive delirium only occurs in less than 2% of the cases (23), while hypoactive and mixed-type delirium have almost the same incidence and are more abundant in delirium patients.

Delirium can be diagnosed using validated tests such as the Confusion Assessment Method for ICU (CAM-ICU) (24). The CAM-ICU method indicates when a patient has a decreased attention and scores the patient either positive or negative to delirium. At the ICU this test is used after every cardiac surgery procedure.

1.3 POSTOPERATIVE COGNITIVE DECLINE

Postoperative cognitive dysfunction (POCD) after cardiac surgery appeared quickly after the introduction of open heart surgery (25). POCD is commonly defined as a disturbance of the neurological function related to surgery (26). In the last few years increasing experience and improved techniques, both surgical as anaesthetic, have led to a general decrease of peri-operative and in-hospital mortality rates to 1-3 % (27). Despite the improving outcome of patients after cardiac surgery, the incidence of postoperative cognitive complications stayed almost unchanged (3). The incidence of POCD at discharge is between 30% and 65%. The incidence of POCD a few months after cardiac surgery is between 20% and 40% (3, 28).

Different brain functions are affected by POCD. The most imported domains affected by POCD are attention, cognitive psychomotor speed, language, learning and memory, and executive functions (26). The cause of POCD is multifactorial, which makes it difficult to be diagnosed in patients. The causes can be: mild ischaemic injury due to microembolisation and/ or regional hypoperfusion, systemic inflammatory response due to major surgery, age and predisposing neurological conditions (29-31).

Because of this multifactorial nature of POCD, the lack of a standardized procedure to measure POCD and the vague definition it is still difficult to predict the exact incidence of POCD (32). Therefore in 1995 the

'statement of consensus on assessment of neurobehavioral outcomes after cardiac surgery' was suggested by Murkin et al. to create more homogeneity in POCD research (33). In this statement of consensus a battery of tests is suggested to test for POCD. This battery of tests consists of four tests (Table 1) which are most reliable to test for POCD. Expect for these tests several other steps need to be performed to reliably test for POCD (33).

Table 1: Battery of neurophysiological tests

Neurophysiologic tests consensus statement	Domain tested
Rey auditory verbal learning test	Verbal Memory
Trail-making A	Attention and processing speed
Trail-making B	Attention and processing speed
Grooved Pegboard	Psychomotor function

1.4 ENDO-CABG

Recently a less invasive way of performing a CABG has been introduced in the field of cardiac surgery. Since 2014, the Jessa hospital, Hasselt, started with an innovative procedure, Endoscopic coronary artery bypass grafting (Endo-CABG), to perform the conventional CABG method in a less invasive way. Endo-CABG is a Minimal invasive way to perform a coronary artery bypass with patients having multivessel disease. This method also avoids the use of a median sternotomy using thorascopic techniques (Figure 1A).

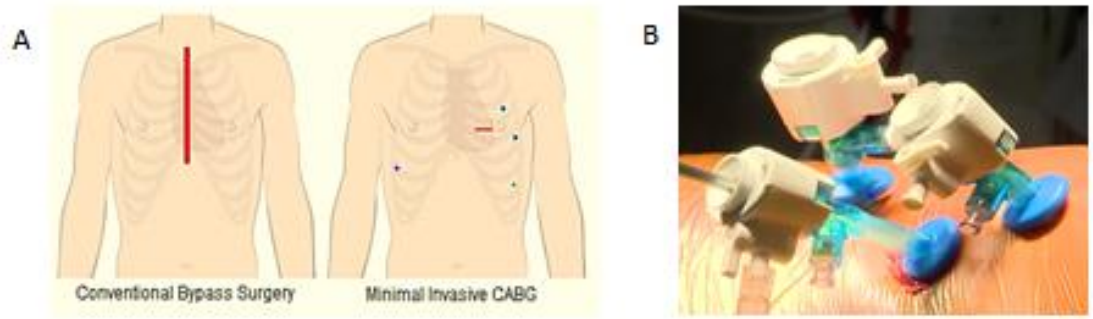

Figure 1: 1A. difference between conventional bypass surgery with sternotomy and minimal invasive CABG. 1B. Thorascopically opened 5-mm holes.

In an Endo-CABG method the conventional sternotomy is avoided by using 3 small 5-mm holes and a 4- to 5-cm incision between the ribs without any mechanical spreading of the ribs. The left internal mammary artery and right internal mammary artery are thoracoscopically opened through the 3 small 5-mm holes (Figure 1A; 1B). Because a heart-lung machine is necessary to perform Endo-CABG, surgeons at the Jessa hospital use a revolutionary minimal invasive extra-corporeal system (Minimal invasive Extra-Corporeal Circulation or MiECC) to perform these Endo-CABG procedures.

Endo-CABG has proven to be feasible and has excellent procedural and short-term outcomes (34). The procedure is used to treat patients with multi-vessel coronary artery disease. Benefits of this procedure include reduced postoperative pain, reduced duration of hospital stay and fast recovery and return to work. However the Endo-CABG procedure provides a better outcome on different outcomes after surgery, there is no certitude it will improve the neurological outcome when compared to conventional coronary artery bypass grafting. Although being less invasive, Endo-CABG method uses retrograde arterial perfusion (RAP). This RAP is associated with a higher incidence of neurological complications, especially in patients with severe (grade IV and V) aortic atherosclerosis (29). In these patient RAP increases the risk of cerebral embolic complications (35). However, postoperative neurocognitive outcome after Endo-CABG has never been studied.

Therefore, the main objective of the neurological outcome after minimal invasive coronary artery surgery (NOMICS) study is to examine neurocognitive outcome and the incidence of neurological complications after Endo-CABG.

The primary objective of the study will be the assessment of the incidence of POCD, CVA and delirium after Endo-CABG. Secondary objectives are:

1. To compare the quality of life (QOL) before Endo-CABG and three months after Endo-CABG.
2. To study patient satisfaction with Endo-CABG.
3. To study patient satisfaction with the performed tests.
4. To study the influence of various demographic and peri-operative variables on neurological outcome after Endo-CABG.
5. To assess the incidence of anxiety before Endo-CABG
6. To compare the incidence of depression before Endo-CABG and 3 months after Endo-CABG.

2. MATERIALS AND METHODS

2.1 STUDY DESIGN

The NOMICS study is designed as a single-centre prospective observational cohort study of 150 patients performed at the JESSA Hospital, Hasselt. The study is being performed in accordance with the declaration of Helsinki and has been approved by the ethics committee of the University of Hasselt and the ethics committee of the JESSA hospital, Hasselt (registration number B243201630254).

2.2 POPULATION

Adult patients undergoing Endo-CABG will be enrolled in the present study (Table 2). Following the recommendations of the '1995 statement of consensus on assessment of neurobehavioral outcomes after cardiac surgery', a comparative group and a healthy control group will be enrolled (Table 2). The groups will be enrolled in a 1:1:1 ratio, which means that 50 subjects are needed per group.

Table 2: The different study groups with the different intervention types.

Group	Intervention
Endo-CABG, surgical group (N=50) (minimal invasive cardiac surgery group)	Procedure/Surgery: Endo-CABG (minimal invasive cardiac intervention) Other names: minimal invasive Coronary Artery Bypass Grafting
PCI, surgical control group (N=50) (comparative minimal invasive procedure)	Procedure/Surgery: PCI (stenting procedure) Other names: percutaneous coronary intervention
Healthy volunteer, control group (N=50) (to exclude learning effect or natural variation in neurological testing)	No intervention This group will be age- and sex-matched

The comparative group consists of patients undergoing an elective percutaneous coronary intervention (PCI). The comparative group is necessary to investigate the different neurological outcomes between Endo-CABG and PCI patients, this will indicate whether the neurological outcome of Endo-CABG patients is related to normal comorbidities in cardiovascular patients or not. The control group consists of volunteers who will not undergo an Endo-CABG or PCI and who have no other major cardiac or neurological deficits or surgery. This group is necessary to eliminate the effect of natural variation on neuropsychological testing and to exclude the learning effect which can occur when repeated neurocognitive testing is performed.

All patients planned for an Endo-CABG or a PCI will be informed prior to their intervention and will be provided with a patient information sheet. Healthy volunteers will be recruited from family of the patients

and health care workers. The control group will be age – and sex-matched to the Endo-CABG group. Patients interested in the study will receive an appointment with the study investigator (F.V.) and will be assessed for eligibility. The detailed eligibility criteria are listed in supplemental table 1 (**Table S1**).

Patients eligible for the study will receive information on the purpose, procedures, and potential risks and benefits of the study. A written informed consent will be obtained of every subject who decides to participate in the study and the subjects will be able to withdraw from the study at any time without consequences for therapy. The study will be performed at a high volume institution (JESSA hospital, Hasselt, Belgium).

2.3 STUDY PROTOCOL

Despite the presence of different studies addressing the problem of neurological complications after cardiac surgery, a standardized protocol to assess the neurological outcome after cardiac surgery is not available. In this study we created a standardized protocol using the recommendations of the '1995 statement of consensus on assessment of neurobehavioral outcomes after cardiac surgery'. This protocol (see supplemental Figure S1) has been submitted to BMJ open for publication.

Outcome measures in the domains of neurological outcome (POCD and Mini Mental State Examination), Quality of life (QOL), patient satisfaction with Endo-CABG and preformed tests, anxiety and depression will be assessed at baseline and three months after intervention or baseline testing (Figure S1). Delirium will be tested at the Intensive Care Unit (ICU) and stroke will be assessed during hospital stay and at the three month follow-up appointment in case of a clinical suspicion. Patients who are unable to visit the hospital for a study appointment for follow-up will be tested at home.

2.4 BASELINE MEASUREMENTS

The Baseline measurements will be performed before surgery takes place, if the subject is in the Endo-CABG group or the PCI-group, or on a predetermined test date. These measurements exist of different steps. Firstly, general data of the patients will be assessed. This data will include: age, gender, body mass index (BMI), highest level of education and medical background. These are important for matching the different groups and to check if the patient is eligible for the neurological testing. It is important that in the Endo-CABG group and the PCI-group the neurological testing will be performed before an intervention has been done. The healthy control group will not receive any surgical intervention.

Secondly, the different psychological parameters, quality of life and the baseline neurological state are tested. Psychological parameters included in this study are depression and fear. As indicated by Murkin et

al. (33) these mood states can influence the outcome of neuropsychological testing. Depression is measured by the CES-D (36) questionnaire. When a patient reaches a score higher then 8, the patient is indicated to be in an increased depression state. Fear or anxiety is measured using the surgical fear questionnaire (SFQ; (37). The questionnaire is divided in two parts: short term fear and long term fear. Both are scored 0-40, giving a combined score between 0-80. Quality of life (QOL) is measured by using the EQ-5D questionnaire (38). Baseline neurological state will be measured by using the mini mental state examination (39). When the score is lower than 24/30 the patient is indicated to have neurological problems and is not eligible for the study.

Lastly, the POCD measurements will be performed. These include the Rey auditory verbal learning test, the trail-making A and B test, the grooved pegboard test, the WAIS-III digit span test and the WAIS-III digit-symbol coding test. These tests will be performed by one researcher in a room with a minimum of distraction for the patient. When the patient is not able to reach the hospital the tests will be conducted at home. A clinical neurological examination will take place before surgery in the Endo-CABG group. This will indicate any underlying neurological deficits not related to surgery. When an underlying pre-existing neurological disorder is discovered the patient will not be eligible for the study and will be excluded at this point.

2.4.1 REY AUDITORY VERBAL LEARNING TEST

The Rey auditory verbal learning test (RAVLT) measures short term memory, verbal learning, susceptibility to interference, retention of information after a certain period of time and recognition memory (40). Originally it was developed by Rey (41), but later it was translated and adapted by different authors from different countries. The RAVLT is sensitive to memory deficiencies found in different groups of patients and is useful in the diagnosis of memory disturbances (42, 43).

In the RAVLT, a list of 15 substantives (List A) is read to the subject five consecutive times (Figure 2). The subject retrieves as many words as possible every time the complete list of 15 words is read. This gives the subject 5 attempts to retrieve and memorize the words. After the fifth attempt a new interference list (List B) of 15 substantives is introduced and read to the subject, followed by its retrieval (attempt B1). After this attempt, the subject is asked to retrieve the words from list A, this time the list is not read to the subject (attempt A6). After a 20-minute interval, the subject has to retrieve list A again (attempt A7) without reading the list.

A	A1	A2	A3	A4	A5	B	B1	A6	A7
Trommel						Boek			
Gordijn						Trein			
Riem						Bloem			
Koffie						Tapijt			
School						Strand			
Ouders						Harp			
Zon						Zout			
Hof						Vinger			
Pet						Appel			
Boer						Schouw			
Zetel						Knop			
Kalkoen						Schaduw			
Kleur						Sleutel			
Huis						Ratel			
Rivier						goud			
Intrusies									
Totalen									

Figure 2: Rey auditory verbal learning test.

2.4.2 TRAIL-MAKING A & B

The trail-making test is a neuropsychological test which is used in different neurological studies to examine the visual attention and task switching in subjects. It is a straight forward test that consist of two parts each constructed that a subject has to connect 25 dots in a predetermined order (Figure 3). The subject has to solve this test as quickly as possible (44). The test is used to test for visual search speed, speed of processing, mental flexibility and executive functioning.

The first part of the test is primarily used to test cognitive processing speed (45). It exists of 25 consecutive numbers (Figure 3A) which have to be connected in a consecutive way (46). The second part of the test is mainly used to test the executive functioning of the subject (45). It exists of both numbers and letters (Figure 3B). The subject has to alternate between numbers and letters in a consecutive way (1-A-2-B, etc.) (46). The completion time of both tests is measured and whenever a subject makes an error this is directly added to the completion time (plus one second per mistake). The trail-making test is commonly used in clinical settings to recognize many types of brain impairment, particularly in the frontal lobe.

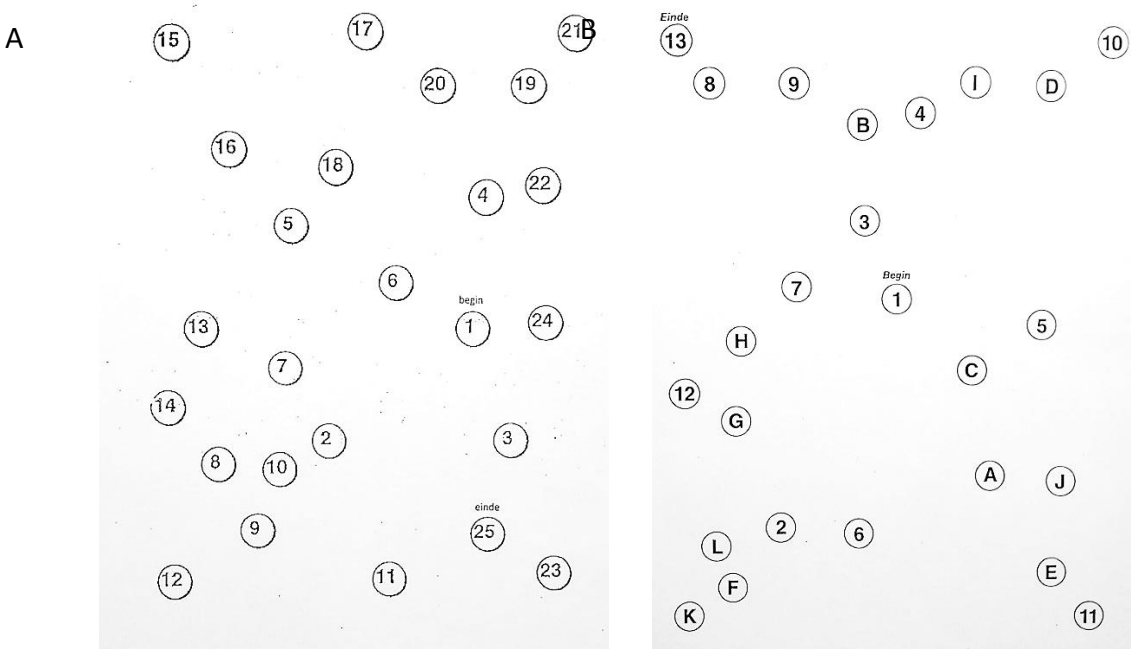

Figure 3: Trail-making A & B. 3A: trail-making part A existing of 25 consecutive numbers. 3B: trail-making part B existing of 25 alternating consecutive numbers and letters.

2.4.3 GROOVED PEGBOARD

The grooved pegboard test is a neurological tool to examine the manual dexterity and complex motor coordination (42). The grooved pegboard test is manufactured by the Lafayette instrument company. It consists of a board containing 25 slotted holes in a 5 x 5 array (Figure 4). The test is designed in a key – keyhole fashion in, this means that the subject has to fit 25 pegs as rapidly as possible in the 25 holes. The first measurement is done by sing the dominant hand, the second measurement the non-dominant hand is used to complete the test.

Figure 4: Grooved pegboard test.

Except for completion speed of the test, other factors are also added to the final score. The amount of correctly placed pegs is also incorporated in the end score of either the dominant or non-dominant score. Also, the amount of pegs dropped during the test will be added to the final test scores. This means that the final test score exists of a sum of the completion time, the amount of correctly place pegs and the amount of pegs dropped (Figure 4).

2.4.4 WAIS-III DIGIT SPAN & WAIS-III DIGIT-SYMBOL CODING

The digit span test is commonly used to test the working memory, and more specific the number storage capacity of working memory. The subject will hear a sequence of digits and is asked to recall this sequence correctly (Figure 5). The sequences start from two digits and can be up to nine digits. The eventual span of a subject is the longest number of sequential digits that can be recalled accurately. The test can be performed in two different ways. First, the researcher reads certain sequences of digits and the subject has to recall the digits in the same order (Figure 5A). This is called the forward digit span. Second, the researcher again reads certain sequences of digits and the subject has to recall the digits in the reverse order (Figure 5B).

A

Cijferreeksen voorwaarts			Score van de pogingen	Itemscore (0, 1 of 2)
Poging		Item/antwoord		
1.	1	1 - 7		
	2	6 - 3		
2.	1	5 – 8 – 2		
	2	6 – 9 – 4		
3.	1	6 – 4 – 3 – 9		
	2	7 – 2 – 8 – 6		
4.	1	4 – 2 -7 – 3 – 1		
	2	7 – 5 – 8 – 3 – 6		
5.	1	6 – 1 – 9 – 4 – 7 – 3		
	2	3 – 9 – 2 – 4 – 8 – 7		
6.	1	5 – 9 – 1 – 7 – 4 – 2 – 8		
	2	4 – 1 – 7 – 9 – 3 – 8 – 6		
7.	1	5 – 8 – 1 – 9 – 2 – 6 – 4 – 7		
	2	3 – 8 – 2 – 9 – 5 – 1 – 7 – 4		
8.	1	2 – 7 – 5 – 8 – 6 – 2 – 5 – 8 – 4		
	2	7 – 1 – 3 – 9 – 4 – 2 – 5 – 6 – 8		
Totale score cijferreeksen voorwaarts (Maximum = 16)				

B

Cijferreeksen achterwaarts			Score van de pogingen	Itemscore (0, 1 of 2)
Poging		Item/antwoord		
1.	1	2 – 4		
	2	5 – 7		
2.	1	6 – 2 – 9		
	2	4 – 1 – 5		
3.	1	3 – 2 – 7 – 9		
	2	4 – 9 – 6 – 8		
4.	1	1 – 5 – 2 – 8 – 6		
	2	6 – 1 – 8 – 4 – 3		
5.	1	5 – 3 – 9 – 4 – 1 – 8		
	2	7 – 2 – 4 – 8 – 5 – 6		
6.	1	8 – 1 – 2 – 9 – 3 – 6 – 5		
	2	4 – 7 – 3 – 9 – 1 – 2 – 8		
7.	1	9 – 4 – 3 – 7 – 6 – 2 – 5 – 8		
	2	7 – 2 – 8 – 1 – 9 – 6 – 5 – 3		
Totale score cijferreeksen achterwaarts (Maximum = 14)				
Voorwaarts + Achterwaarts =			(Maximum = 30)	

Figure 5: WAIS-III digit span test. 5A: Digit span forward, reflection of digits in same order. 5B: Digit span backward, reflection of digits in reverse order.

The digit symbol coding test is commonly used to test for the processing speed, associative memory and graphomotor speed of a certain subject. The digit symbol test is sensitive to brain damage, age and depression. The test consists of nine digit-symbol pairs, which is followed by a list of random digits between one and nine (Figure 6). The subject has to couple the right symbol to the right digit in a consecutive fashion. The test is time limited, which means that the subject has 120 seconds to correctly write down as many consecutive symbols as possible. The number of correct symbols written down in 120 seconds is the final score of the test.

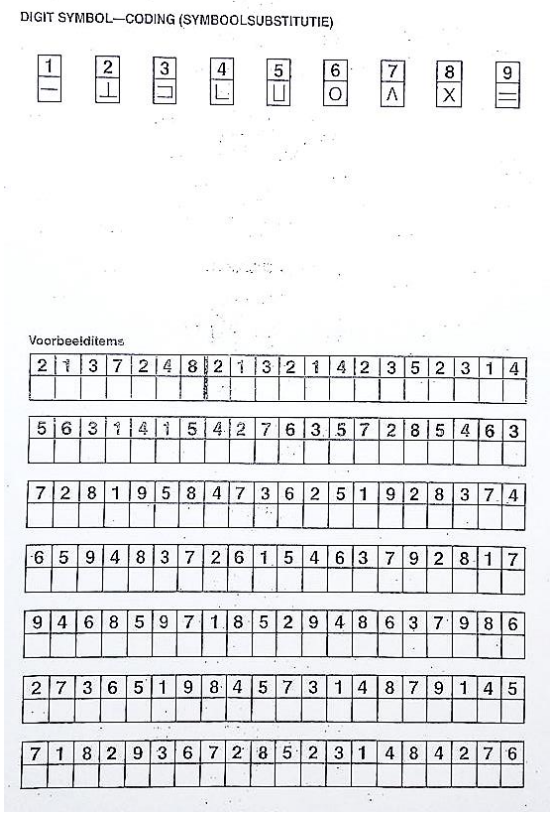

Figure 6: WAIS-III Digit-symbol coding test.

2.5 POSTOPERATIVE MEASUREMENTS

After the baseline measurements two groups will undergo cardiac surgery (Endo-CABG and PCI) and one group will not undergo any surgery (Healthy control). For the Endo-CABG group several tests will performed shortly after surgery. This group will undergo a clinical neurological investigation to check for any neurological disorders postoperatively. Also delirium will be checked. This is a standard procedure and will be done using the CAM-ICU (confusion assessment method for the intensive care unit) (47). When there is an indication for CVA, an MRI or CT scan will be made to diagnose the CVA and the severity.

Three months after surgery (Endo-CABG and PCI group) or three months after the baseline measurements, the subjects will undergo almost the same neurological tests performed in the baseline testing. Before testing the subject the eligibility of the patient is checked. When the subject still meets the eligibility criteria, the follow-up can be started.

The first step is the assessment of the psychological state of the patient using the depression questionnaire (CES-D questionnaire). Also, the quality of life at this particular time is assessed using the quality of life questionnaire (EQ-5D). Next, the different neurological tests (Rey auditory verbal learning test, Trail-making A & B, etc.) will be performed to receive data which can be compared with the baseline data. Also patient

satisfaction about the surgery and the tests performed are collected. This is done by a short questionnaire of 3 questions that use the 1-10 scale. After this the patient has completed the study and data can be analysed.

2.6 PERIOPERATIVE MANAGEMENT

All patients in the Endo-CABG group will be treated following a uniform, standardized protocol for anaesthesia, surgical techniques and extracorporeal circulation to reduce treatment heterogeneity within the study groups (see appendix). This protocol includes recently recommended neuroprotective methods in an attempt to minimize the risk of poor neurological outcome after cardiac surgery.

STATISTICAL ANALYSIS

POCD is defined as a decline in performance on neuropsychological assessment between baseline and 3-month follow-up beyond natural variation and learning effects. We used the Reliable Change Index (RCI) to control for natural variation or in other words, the test-retest variability inherent in a matched normative data set (26). The RCI or z-score provides an estimate of the probability that a patient´s change in test score is reliable and not due to chance (26). The learning effect occurs because repeated administration of a test increases the knowledge of the test structure and thus performance tends to improve with repeated administration (48). We used a healthy control group to control for learning effects and natural variation. We used a PCI group to separate the effects of surgery from those of underlying disease.

The individual RCI scores will be calculated as follows: for each patient, the baseline score from each test will be subtracted from the follow-up score, giving Δx. The same will be done in the control group, giving Δxc. The mean change on that test in the control group will then be subtracted from Δx to eliminate practice effects. This result will then be divided by the standard deviation of Δxc to eliminate the effect of natural variation in test performance. This is called a Z-score. The RCI is defined as the sum of the Z-scores of all tests. The difference score is computed such that a positive change reflects improvement and vice versa.

POCD in an individual patient is defined as an RCI ≤ −1.645 or RCI ≥ 1.645 (significance level 5%), or Z-score ≤ −1.645 or ≥ 1.645 in at least two different tests. In some tests a negative score means a decrease in function, but the tests which use a time indication as a score will need a positive difference to show a decrease in function.

Stroke is defined as a new neurologic deficit presenting in hospital combined with signs of recent ischemic cerebral infarction on brain CT or MRI. Patients with a postoperative stroke within the 3-month observation period were automatically also classified in the POCD group.

Delirium is defined by the CAM-ICU test and the result will be dichotomised. The quality of life will be tested using a Mann Whitney U test at significance level 5%. The group RCI scores will be compared using ANOVA or Kruskal-Wallis.

3 RESULTS AND DISCUSSION

3.1 POPULATION

3.1.1 POPULATION CHARACTERISTICS

In total 91 patients were already included in the study. Inclusion is still going on and will go on beyond the scope of this report. This report will show preliminary data for the 91 patients included in the study. In Figure 7 the inclusion flow chart shows that from a total of 158 screened patients, 91 patients were included. These patients completed the baseline tests before undergoing surgery (Endo-CABG and PCI group) or at the baseline point (Control group). After this baseline point seven patients were excluded due to loss of follow-up, surgical events or new medical treatments. This means a total of 84 patients can participate the follow-up testing. From this group of 84 patients, 31 patients have already reached the follow-up point. This group completed the follow-up tests three months after surgery or after completing the baseline tests (control group).

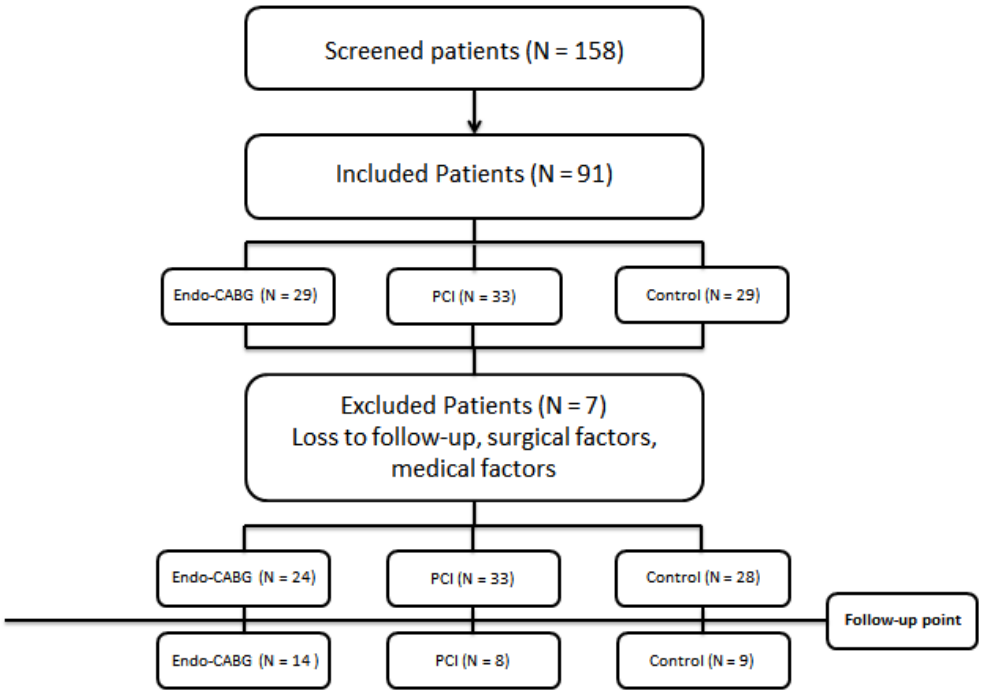

Figure 7: flowchart Inclusion and exclusion of patients.

The patients were enrolled at different departments of the Jessa hospital. The Endo-CABG patients were included at the department of cardiothoracic surgery. The patients undergoing an Endo-CABG treatment visited their surgeon (Dr. A. Yilmaz) at the preoperative consultation. Here the patients were informed about the study and a date for baseline measurement was determined. Healthy controls were also enrolled

at the department of cardiothoracic surgery. This was done by enrolling family or friends of the Endo-CABG patients. PCI patients were included before receiving the intervention or were included before receiving a coronary angiography, which is a catherisation method using contrast fluid to examine the coronary arteries. Healthy controls were also included from this group of patients who received a coronary angiography. Here the result of this examination indicated the patient had no occlusion of the arteries and can be considered as a healthy control. The healthy control patients were included in three different groups (Figure 8): family or relatives Endo-CABG and PCI (N= 8), post-examination healthy subjects (N= 16), and family and relatives of the researcher (N= 4).

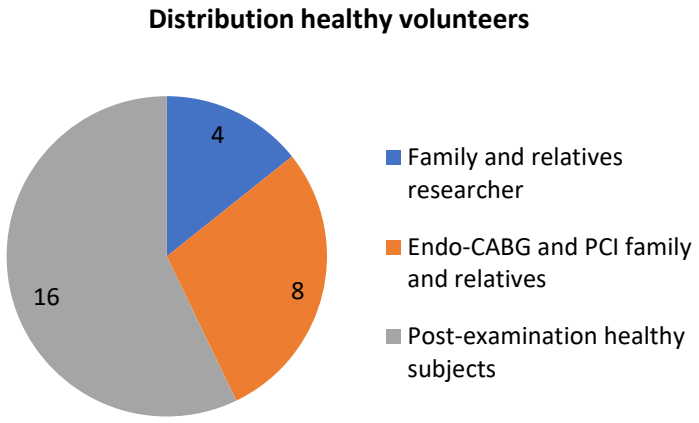

Figure 8: Distribution inclusion healthy volunteers.

Different patient characteristics were measured, including: Gender, Age, Length, Weight, BMI, Profession, education and medical background. Profession and education are included to examine the effect of these variables on the baseline measurement scores. Age and education are variables that can influence neurological test scores (49). Generally higher education and younger age score significantly higher on cognitive tests. Also medical background was included in the patient characteristics. Because of the higher age of the study population medical comorbidities are almost inevitable. Several cardiovascular intervention and comorbidities are seen in the different groups. These include cardiac arrhythmias, PCI interventions, hypertension and several other comorbidities. This is important to exclude the effect of previous interventions on the present study neurological outcome scores. Likewise, neurological and respiratory history of the patient is included to exclude the effect of these factors on the neurological test scores performed in this report. The different patient characteristics of the different study groups are listed in Table 3.

Table 3: population characteristics:

characteristics	Endo-CABG	PCI	Healthy control
N	24	33	28
Gender:			
Male	21	29	21
Female	3	4	9
	Mean (std.)	Mean (std.)	Mean (std.)
Mean Age (y)	66.3 (10.7)	67.61 (10.63)	64.2 (8.8)
Mean Length (cm)	171.42 (8.42)	175.18 (6.64)	172.03 (7.59)
Mean Weight (Kg)	80.41 (12.72)	81.68 (12.44)	80.84 (16.65)
Mean BMI	27.3 (3.78)	26.66 (4.13)	27.2 (4.88)
Profession:			
Retired	17	26	17
Paid employee	5	7	8
Independent	1	0	2
Incapacitated (> 6 months)	0	0	1
Unemployed	1	0	0
Education:			
Primary education	1	0	3
Lower secondary	1	11	4
Higher secondary	15	17	14
Graduate school	6	4	6
University	1	1	1
Medical Background:			
Cardiovascular	5	16	12
Respiratory	1	3	3
Neurological	2	5	7
other	5	4	3

BMI = Body Mass Index (weight/ (length (m))^2), std. = Standard Deviation

3.1.2 INTER-GROUP DIFFERENCES

Before analysing the population, normality was assessed for all parameters (. Data was considered to be normally distributed if the Shapiro-Wilk statistic indicated a value higher than 0.9. Data lying in the range of 0.8-0.9 were indicated as a 'border zone', and are only assumed to be normally distributed if the p-value was higher than 0.05. Because these conditions were fulfilled, the data was considered to be normally distributed and parametric tests can be used to analyse the baseline data. To compare the results of the different groups, we have to examine the group differences and exclude that these differences are significant. Therefore the different baseline characteristics (Table 3) are compared using a one-way ANOVA at a 0.5% significance level. The three different groups show no significant differences for the different

characteristics (Age, length, weight, BMI), which indicates there are no specific differences between the three study groups.

Table 4: One way ANOVA analysis of the different population characteristics.

characteristics	Endo-CABG	PCI	Healthy control	One-way ANOVA
	Mean (std.)	Mean (std.)	Mean (std.)	P-value
Mean Age (y)	66.3 (10.7)	67.61 (10.63)	64.2 (8.8)	0.425
Mean Length (cm)	171.42 (8.42)	175.18 (6.64)	172.03 (7.59)	0.128
Mean Weight (Kg)	80.41 (12.72)	81.68 (12.44)	80.84 (16.65)	0.942
Mean BMI	27.3 (3.78)	26.66 (4.13)	27.2 (4.88)	0.818

BMI = Body Mass Index (weight/ (length (m))^2), std. = Standard Deviation

3.2 BASELINE MEASUREMENTS

3.2.1 MEAN NEUROLOGICAL TEST SCORES AND INTER-GROUP DIFFERENCES

After patients were included in the study and the patient characteristics were collected, the subject was submitted to a range of neurocognitive tests. This baseline data is collected as a baseline value which will be compared to a follow-up value three months after surgery or three months after the first encounter. The subject also performed different test to measure fear before surgery, depression and quality of life. The data of these questionnaires and neurocognitive tests are shown in Table 5 . Here the group means of the different tests are shown together with the standard deviation. Also the different scores have been compared between the Endo-CABG group, the PCI group and the healthy volunteer group. This was done using a One-way ANOVA at significance level 5%. This gives an indication if there is a significant difference between the three groups. When the P-value is lower than 0.05 the group means differ significantly from each other.

When comparing the different group using One-way ANOVA, no significant difference can be found between the different test groups (Table 5). The only difference that can be found is in the preoperative fear tests. More specifically in short term fear scores. Here the scores of the PCI group are significantly lower. Because the Fear before surgery test is not included for the healthy volunteer there are no values for this group. Therefore the fear scores of the Endo-CABG and PCI group were also compared using an unpaired T-test. This test also indicates a p-value of 0.013 and thus shows a significant difference in short term fear between the Endo-CABG and PCI Group. This shows that before and Endo-CABG subjects tend to have more fear than subject who will receive a PCI. The other results indicate that at the baseline point there is no significant difference between the three test groups.

Table 5: Mean neurocognitive test results and One-way ANOVA analysis

Baseline measurement	Endo-CABG	PCI	Healthy volunteer	One-way ANOVA
	Mean (std.)	Mean (std.)	Mean (std.)	P-value
Fear (SFQ, short term)	16.29 (7.056)	11.12 (7.829)	/	0.013*
Fear (SFQ, long term)	11.83 (6.281)	10.61 (8.627)	/	0.557
Total Fear (SFQ)	28.13 (11.199)	21.73 (15.123)	/	0.086
Depression (CES-D)	7.5 (5.971)	6.88 (5.023)	6.89 (5.580)	0.898
Quality of life (EQ-5D-5L)	7.13 (2.193)	7.21 (3.018)	7.04 (2.742)	0.969
MMSE	28.5 (1.251)	27.79 (1.980)	28.14 (1.604)	0.289
Rey auditory verbal learning:				
A1	4.83 (1.786)	4.12 (1.763)	4.57 (1.952)	0.334
A2	7.25 (2.172)	6.55 (2.611)	7.61 (2.807)	0.262
A3	9.08 (2.263)	7.82 (2.604)	9.32 (3.080)	0.068
A4	9.58 (2.992)	8.88 (2.724)	10.21 (3.071)	0.209
A5	10.58 (2.603)	9.79 (3.305)	10.79 (3.059)	0.402
B1	4.46 (1.744)	3.76 (1.786)	4.46 (1.915)	0.226
A6	8.08 (2.858)	7.09 (3.521)	8.68 (4.146)	0.221
A7	8.42 (3.120)	6.88 (3.533)	8.64 (4.156)	0.127
Total Rey (sum of attempts)	62.29 (16.594)	54.88 (18.643)	64.29 (21.534)	0.134
Proactive interference (B1/A1)	1.05 (0.608)	1.039 (0.825)	1.19 (0.917)	0.710
Retroactive interference (A6/A5)	0.768 (0.2)	0.713 (0.278)	0.767 (0.247)	0.617
Forgetting speed (A7/A6)	1.045 (0.156)	1.02 (0.349)	1.021 (0.22)	0.931
Trail-making A (Sec)	43.38 (1.368)	47.24 (24.787)	36.86 (15.224)	0.128
Trail-making B (sec)	119.5 (62.771)	135.33 (76.403)	101.54 (49.974)	0.134
WAIS-III Digit span	15.29 (4.091)	13.88 (4.114)	14.46 (4.282)	0.453
WAIS-III Digit-Symbol coding	59.5 (18.875)	50.94 (17.855)	60.82 (20.085)	0.092
Grooved pegboard (dominant, sec)	119.38 (23.402)	128.64 (27.894)	114.04 (30.427)	0.118
Grooved pegboard (non-dominant, sec)	130.67 (34.373)	141.76 (39.641)	121.89 (29.039)	0.091

*A and B = attempts on ray auditory verbal learning, Sec = seconds, proactive interference = old information interferes with new information, retroactive interference = new information interferes with old information, *significant difference at significance level 0.05*

3.2.2 EFFECT OF AGE ON NEUROCOGNITIVE TEST PERFORMANCE

As mentioned earlier, age has an effect on neurocognitive test results (49). In this section we are going to examine the effect of age on the study test battery. Because we could not find significant differences between the different groups we will not differentiate the groups by intervention. The groups will be

divided into four categories (]40– 55], [56-65], [66-75], [76-85[). Again the data will be compared using One-way ANOVA to check difference between the different age categories.

Table 6: Mean values neurocognitive tests in age dependent categories and one way ANOVA analysis.

Age effect	**[40-55]**	**]55-65]**	**]65-75]**	**]75-88]**	**ANOVA**
	Mean (std.)	Mean (std.)	Mean (std.)	Mean(std.)	P-value
N	14	28	27	16	
Total Rey	72.14 (15.95)	65.18 (20.31)	55.93 (17.043)	47.56 (15.8)	0.001*
Proactive interference	0.912 (0.24)	1.218 (0.93)	1.119 (0.94)	0.997 (0.61)	0.617
Retroactive interference	0.807 (0.19)	0.776 (0.21)	0.709 (0.28)	0.703 (0.29)	0.604
Forgetting speed	1.055 (0.12)	0.969 (0.19)	1.067 (0.30)	1.04 (0.38)	0.547
Trail-making A (sec)	30.93 (11.93)	36.79 (20.23)	44.74 (16.69)	60.06 (19.56)	<0.001**
Trail-making B (sec)	90.43 (57.63)	92.39 (42.76)	126.67 (59.09)	181.5 (74.63)	<0.001**
WAIS-III digit span	16.36 (5.5)	14.82 (4.09)	14.19 (3.96)	12.69 (2.44)	0.107
WAIS-III digit symbol	72.86 (16.97)	60.89 (18.76)	53.81 (16.62)	39.63 (10.26)	<0.001**
Grooved pegboard (Dominant; sec.)	104.29 (17.06)	113.79 (31.14)	121.85 (20.75)	147.94 (22.62)	<0.001**
Grooved pegboard (non-dominant; sec.)	105.79 (20.18)	123.29 (34.66)	130.26 (24.6)	173.56 (29.84)	<0.001**

*Sec = seconds, proactive interference = old information interferes with new information, retroactive interference = new information interferes with old information, *significant difference at significance level 0.05, ** significant difference at significance level 0.01*

As indicated in Table 6, different neurological tests are influenced by age. Especially the time dependent neurocognitive tests like the grooved pegboard, WAIS-III digit symbol coding and Trail-making test show significant differences between the age categories. This indicates that at younger age the processing speed and concentration level is faster than at higher ages. Also the Rey auditory verbal learning test shows this difference. This test reflects on the short term verbal memory. Again, the younger age categories score significantly better ($p = 0.01$) better in the Rey auditory verbal learning test. This indicates that the working short term memory is much more accessible for the younger age categories.

3.2.3 EFFECT OF EDUCATIONAL LEVEL ON NEUROCOGNITIVE TEST PERFORMANCE

Together with age, education is a factor that has a great impact on neurocognitive test performance (49). We divided the total data of all patients into five groups (Table 7): primary education, lower secondary, higher secondary, graduate school and university. These are the five main educational levels a subject could have had in the past. The different baseline test scores will be compared between these five categories. Differences between these groups will be identified using a Kruskal-Wallis comparison. Here a non-parametric test is used because we cannot use the one-way ANOVA because we have three groups with small population size.

Table 7: Different educational levels and mean test scores per educational level

Education	**Primary education**	**Lower secondary**	**Higher secondary**	**Graduate school**	**University**
	Mean (std.)	Mean (std.)	Mean (std.)	Mean (std.)	Mean (std.)
N	4	16	46	16	3
Total Rey	42.75 (16.32)	50.06 (19.52)	58 (15.86)	76.31 (16.46)	81.67 (22.03)
Proactive interference	0.99 (0.68)	0.88 (0.44)	1.22 (1.00)	1.03 (0.37)	0.74 (0.13)
Retroactive interference	0.77 (0.09)	0.76 (0.35)	0.73 (0.24)	0.77 (0.19)	0.86 (0.24)
Forgetting speed	1.12 (0.16)	0.96 (0.35)	1.04 (0.27)	1.07 (0.15)	0.91 (0.31)
Trail-making A (sec.)	47.75 (13.2)	58.69 (25.45)	40.33 (17.61)	34.63 (14.22)	31.00 (17.35)
Trail-making B (sec.)	143 (61.76)	152.56 (72.03)	124.8 (66.29)	72.38 (25.08)	88.33 (56.04)
WAIS-III digit span	11.75 (1.26)	11.94 (2.35)	14.37 (3.81)	17.19 (4.74)	18.67 (5.77)
WAIS-III digit symbol	36.5 (5.92)	41.38 (14.94)	56.87 (15.47)	71.94 (17.63)	79.0 (28.05)
Grooved pegboard (dominant; sec.)	129.0 (17.05)	137.56 (40.2)	118.70 (22.43)	111.25 (24.41)	115.33 (36.36)
Grooved pegboard (non-dominant; sec.)	137.0 (17.57)	149.69 (44.30)	126.61 (29.49)	131.88 (42.97)	116.67 (31.18)

Sec = seconds, proactive interference = old information interferes with new information, retroactive interference = new information interferes with old information

As expected the educational level of the test subjects has a significant effect on several neurocognitive tests (Table 8). Again the more time dependent tests (Trail-making A & B, WAIS digit symbol coding) show significant differences between the educational levels. But also memory tasks give a significant difference between the different educational groups. For the Rey auditory verbal learning test a p-value smaller than 0.001 is detected. Also for the WAIS-III digit span test a p-value of 0.004 is detected. Therefore, educational level can be expected to be a factor that influences neurocognitive test results.

Table 8: Kruskal-Wallis analysis of educational effect on neurocognitive baseline scores.

Education	Kruskal-Wallis (p-value)
Total Rey	<0.001**
Proactive interference	0.66
Retroactive interference	0.793
Forgetting speed	0.348
Trail-making A (sec.)	0.014*
Trail-making B (sec.)	0.001*
WAIS-III digit span	0.004*
WAIS-III digit symbol	<0.001**
Grooved pegboard (dominant; sec.)	0.159
Grooved pegboard (non-dominant; sec.)	0.336

*Sec = seconds, proactive interference = old information interferes with new information, retroactive interference = new information interferes with old information, *significant difference at significance level 0.05, ** significant difference at significance level 0.01*

3.2.4 EFFECT OF FEAR AND DEPRESSION ON NEUROCOGNITIVE TEST PERFORMANCE

Psychological status of a subject undergoing neurocognitive examination has been indicated as a factor affecting the baseline scores of neurocognitive testing (33). In this study both fear before an operation and overall depression status are included in the test battery. In this section the effect of these factors on the performance of subjects on the different neurocognitive tests will be examined.

Firstly, we will look at the effect of different fear gradations on the test scores of neurocognitive tests. Because the healthy volunteer group did not receive any surgery or surgical intervention in the scope of this study, this test group will not be examined for fear before surgery. The subjects will be divided into three categories depending on the total fear test scores: total fear [0-20], total fear [21-40] and total fear [41-63]. The data will be compared using One-way ANOVA.

In Table 9 the different mean neurocognitive test scores are showed for the different Fear categories. The p-values for the one-way ANOVA are also showed. These p-values indicate that there is no significant effect of fear on the selected Neurocognitive test battery. This indicates that fear before operation in this test group has no effect on the tests scores. This can be due to the fact that overall fear before surgery is low (49 out of 57 score below 41/80). This shows us that the overall scores on the neurocognitive tests were not affected by their fear status at the moment of baseline testing. This indicates that, although short term fear in the Endo-CABG group is still significantly higher (p = 0.013) compared to the PCI group, the overall

fear of subjects undergoing minimal invasive cardiac surgery does not affect their neurocognitive performance.

Table 9: Different Total fear scores and mean test scores. Anova analyses of different fear categories and test scores

Fear	Fear [0-20]	Fear [21-40]	Fear [41-80]	Anova
N	25	24	8	
	Mean (std.)	Mean (std.)	Mean (std.)	p-value
Total Rey	57.72 (17.97)	59.67 (19.39)	53.88 (15.23)	0.737
Proactive interference	0.831 (0.401)	1.10 (0.601)	1.54 (1.462)	0.052
Retroactive interference	0.772 (0.25)	0.74 (0.261)	0.61 (0.169)	0.275
Forgetting speed	0.981 (0.324)	1.09 (0.255)	1.01 (0.207)	0.406
Trail-making A (sec.)	47.92 (22.94)	42.58 (19.09)	47.5 (25.75)	0.671
Trail-making B (sec.)	130.64 (60.15)	129.29 (79.74)	120.63 (82.12)	0.942
WAIS-III digit span	14.2 (3.84)	15.46 (4.54)	12.38 (3.07)	0.171
WAIS-III digit symbol	52.56 (17.55)	57.13 (19.58)	53 (20.47)	0.678
Grooved pegboard (dominant; sec.)	125 (22.26)	125.71 (31.32)	121 (24.21)	0.909
Grooved pegboard (non-dominant; sec.)	139.28 (36.58)	135.5 (39.86)	135 (38.34)	0.929

Sec = seconds, proactive interference = old information interferes with new information, retroactive interference = new information interferes with old information

Secondly, the depression state of subjects undergoing neurocognitive testing can affect their test scores (33). This will be tested by dividing the different subjects into different depression state categories, according to their depression test scores. The subjects will be divided into two groups: depression score [0-10] and depression score [11-21]. The different scores will be compared using an unpaired T-test.

In Table 10 the different mean neurocognitive test scores of the different depression categories are shown. Because the overall low depression scores (maximum depression score = 21/80) no differences are seen between the different depression categories. This indicates that in this study the effect of depression on the different neurocognitive tests is limited. This can be seen in the different p-values for the different tests. No significant differences were found. This indicates that the overall depression score of patients undergoing minimal invasive cardiac surgery will not affect the neurocognitive test performance of these subjects.

The overall effect of fear and depression in this study is limited. No significant effects could be indicated. This means that Fear and depression bias will not affect the RCI scores after follow-up neurocognitive test scores are added to the equation.

Table 10: Different depression categories and mean scores. Unpaired T-test analysis of the different depression categories and test scores

Depression	Depression [0-10]	Depression [11-21]	Unpaired T-test
N	62	22	
	Mean (std.)	Mean (std.)	p-value
Total Rey	62.5 (18.61)	54.86 (19.62)	0.107
Proactive interference	1.06 (0.702)	1.25 (1.014)	0.339
Retroactive interference	0.763 (0.239)	0.733 (0.224)	0.600
Forgetting speed	1.04 (0.253)	1.00 (0.293)	0.610
Trail-making A (sec.)	42.65 (19.77)	43.95 (21.56)	0.872
Trail-making B (sec.)	120.53 (68.85)	120.27 (57.38)	0.987
WAIS-III digit span	14.71 (4.12)	13.91 (4.34)	0.442
WAIS-III digit symbol	57.87 (19.73)	53.23 (18.18)	0.336
Grooved pegboard (dominant; sec.)	123.06 (30.14)	116.18 (21.41)	0.328
Grooved pegboard (non-dominant; sec.)	133.84 (35.44)	127.27 (37.14)	0.463

Sec = seconds, proactive interference = old information interferes with new information, retroactive interference = new information interferes with old information

3.3 FOLLOW-UP MEASUREMENTS

3.3.1 POSTOPERATIVE INCIDENCE OF DELIRIUM AND CEREBROVASCULAR ACCIDENT

The incidence of Delirium is tested three to four days after surgery at the intensive care unit. This is tested by the CAM-ICU test and gives a straight forward result. When a patient meets the criteria for delirium, this patient will be diagnosed with delirium and has to stay for a prolonged time in the hospital. When none of the tested criteria is found or when the test score is lower than a predetermined baseline score, the subject has no delirium.

This test was performed on all Endo-CABG subjects (N=24) after surgery. The patients remained at the Intensive care unit for 3-4 days. A subject without delirium had a score of zero and a patient with delirium was given a score of one. All subjects included were checked for delirium and no delirium was found in the Endo-CABG patients. The PCI and healthy control groups Delirium were not tested because of an absence of general anesthesia (local anesthetics in PCI), or because no surgery was done (healthy control).

Postoperative stroke is diagnosed when there is an indication for stroke. When an indication is found the subject will undergo an MRI or CT scan to diagnose the damage. Postoperative stroke can be a direct consequence of surgery. In the scope of this study a patient with stroke is automatically placed in the POCD (postoperative cognitive dysfunction group) and will not be assessed at the follow-up point. In the healthy control group stroke willnot be diagnosed as postoperative stroke but will be classified as an neurological accident. A subject from the healthy group with a stroke will be excluded from the study. In Figure 9 the number of subjects diagnosed with postoperative stroke are shown. We see that this number is the same for the Endo-CABG and PCI group. As expected no Stroke is found in the healthy volunteer group. For the endo-CABG group 1/24 (4.16%) subjects suffered from stroke. In the PCI group this is 1/33 (3.03%).

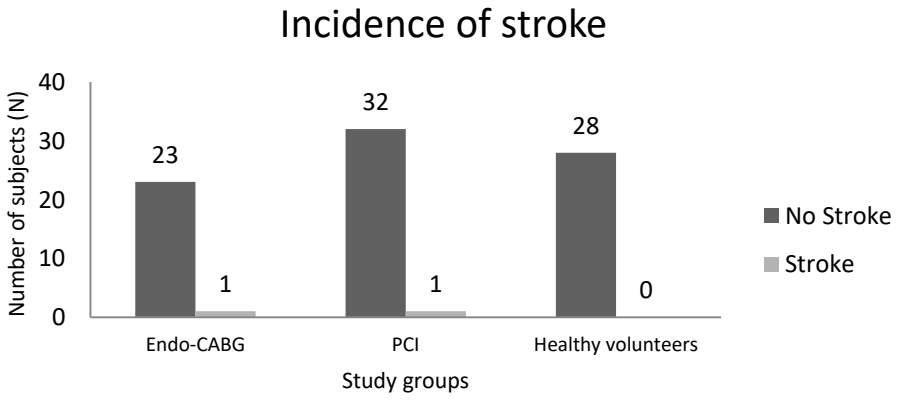

Figure 9: Incidence of Stroke in different study groups.

3.3.2 INCIDENCE OF POSTOPERTIVE COGNITIVE DYSFUNCTION (POCD) AFTER CARDIAC SURGERY

The incidence of postoperative cognitive dysfunction (POCD) is tested three months after baseline testing or after surgery. Subjects who suffered from Cerebrovascular accident (CVA or stroke) or delirium are also indicated to have POCD and are automatically categorized in this group. POCD is diagnosed using Z-scores. This score is calculated using the equation [1]. Here Δx is the individual difference between the follow-up score and the baseline score for a particular test. Δxc is the mean difference between healthy control follow-up scores and baseline scores. And SDxc is the standard deviation of the differences of the healthy volunteer follow-up scores and baseline scores. SDxc coorigates for the learning effect that can be present after neurocognitive testing. This gives us an individual Z-score (Zx) for each subject.

$$Zx = \frac{\Delta x - \Delta xc}{SDxc} \quad [1]$$

POCD is diagnosed in a subject when the individual Z-scores of two or more tests is either ≤ -1.645 (Rey auditory verbal learning test, WAIS-III digit span and WAIS-III digit symbol coding) or ≥ 1.645 (Trail-making A

& B, Grooved pegboard dominant and non-dominant)at a significance level of 5%. The group RCI score is the sum of all individual Z-scores in one group, divided by the SD of this sum in the control group.

In the previous section in both the Endo-CABG and PCI group one subject was diagnosed with CVA. This means that these patients are automatically classified as POCD subjects. The other subjects were tested at the follow-up point. After these tests the individual Z-scores were calculated and the subjects suffering from POCD could be identified. Normality tests (Shapiro-Wilk) inidicated normallity for the different Z-Scores in the three groups.

There are three different outcomes possible in this study. Subjects can have an significantly improved or decreased score or have an unchanged score on the different neurocognitive tests. When the Z-score of a specific patient on a specific neurocognitive test is ≤ -1.645 or ≥ 1.645 (depending of the neurocognitive test performed) the subjects are indicated to be significantly improved or worsened on a specific test (Table 11).

Table 11: Change in test score after follow-up tests in the different test groups.

Neurocognitive tests	Endo-CABG	PCI	Healthy control
N	13	7	9
Rey (total)			
Unchanged	12	7	9
Improved	1	0	0
Worsened	0	0	0
Trailmaking A			
Unchanged	13	6	8
Improved	0	1	1
Worsened	0	0	0
Trailmaking B			
Unchanged	11	5	7
Improved	0	0	1
Worsened	2	2	1
WAIS-III digit span			
Unchanged	10	5	8
Improved	1	2	0
Worsened	2	0	1
WAIS-III digit symbol coding			
Unchanged	9	6	8
Improved	2	0	0
Worsened	2	1	1
Grooved pegboard (Dominant)			
Unchanged	13	6	8
Improved	0	0	1
Worsened	0	1	0
Grooved pegboard (non-dominant)			
Unchanged	8	6	8
Improved	5	1	1
Worsened	0	0	0

The improved and worsened scores were results from the analysis of the different Z-scores of the subjects on the different tests. Significant differences were seen when an individual Z-score was ≤ -1.645 of or ≥ 1.645 depending on the test used.

In Table 11 the different results of the subjects are showed when we compare the follow-up score with the baseline score. As expected in the PCI and healthy control group, most subject follow-up scores were unchanged or even improved compared to the baseline scores. In the Endo-CABG group this result is also shown. Mainly in the WAIS-III digit span and digit-symbol coding tests and the trail-making B test subjects showed significantly worsened scores.

A subject is diagnosed with POCD when a specific subject scored significantly worse on ≥ 2 neurocognitive tests or when an individual is diagnosed with delirium or Stroke. In Figure 10 the amount of subjects suffering from POCD in the different groups are showed. We see that in the PCI and Endo-CABG groups the same number of patients suffer from POCD. Because this is only a preliminary report on the incidence no conclusive differences are seen but data suggest that the neurological outcome of Endo-CABG and PCI groups are similar. As expected no subjects in the healthy volunteer group are suffering from POCD, stroke or delirium. For the endo-CABG group this preliminary result indicates that 2/14 (14.3%) suffers from POCD. For the PCI group this is 2/8 (25%). These results are only preliminary so no major conclusion can be drawn from these numbers. They only give us an indication whether POCD numbers are similar between the endo-CABG group and the PCI group.

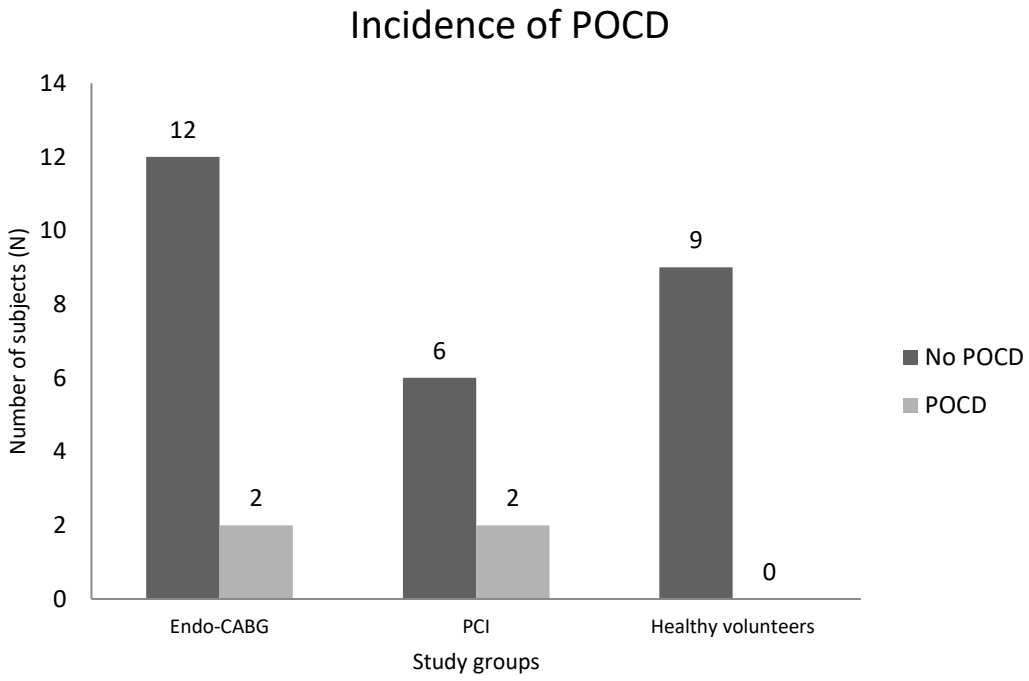

Figure 10: Incidence of POCD in the different study groups

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3.3.3 DIFFERENCES IN RCI SCORES BETWEEN THE ENDO-CABG AND PCI GROUP

The RCI scores of the different tests and the total RCI of the different groups can also be compared. This will give an indication about the difference in neurocognitive test results between the different groups. A RCI score can be calculated by taking the mean of all Z-scores of a particular test. In the same way the group RCI can be calculated by calculating the mean of all RCI scores. In time related tasks, lower scores reflect better performance. For these groups the Z-scores were inverted so that positive RCI values always indicate improvement and negative RCI values indicate decline in test performance.

In this section the different RCI scores of the Endo-CABG and the PCI group will be compared. This will be done to check the difference in neurocognitive outcome tests between these groups. Because of the low population sizes of both groups the data will be analysed using a Mann-Whitney U test.

Table 12: Differences in RCI scores for different neurocognitive tests.

Neurocognitive tests	Endo-CABG	PCI	p-value
Rey (Total)	-0.209 (0.976)	-0.091 (0.947)	0.721
Trail-making A	0.05 (0.696)	-0.465 (0.744)	0.321
Trail-making B	0.396 (1.163)	1.595 (2.687)	0.361
WAIS-III digit span	-0.82 (1.186)	1.492 (1.771)	0.045*
WAIS-III digit-symbol coding	-0.333 (1.623)	-0.411 (1.558)	0.781
Grooved pegboard (dominant)	-0.086 (0.601)	0.232 (1.127)	0.721
Grooved pegboard (non-dominant)	-0.956 (1.163)	-1.223 (2.469)	0.662

**significant at significance level 5%.*

In Table 12 the different RCI scores for the neurocognitive tests were compared between the Endo-CABG group and the PCI group to find any group specific differences. Only the RCI scores for the WAIS-III digit span showed significant difference ($p = 0.045$). The PCI group significantly improved on this test compared to the Endo-CABG. The other RCI scores showed no significant difference in RCI scores. This indicates that the test performances of the Endo-CABG and PCI group are comparable.

Next the group difference in RCI score is compared between the Endo-CABG and PCI group. In Figure 11 the boxplot output is given of the different RCI scores and the subsequent group means of the Endo-CABG and PCI group. When we compare the mean Group RCI, no significant difference can be found ($p = 0.949$). The difference was tested using a Mann-Whitney U test with a significance level of 5%. This confirms the before mentioned results of the RCI scores of the different neurocognitive tests. The results of the Endo-CABG subjects and PCI subjects are comparable and no overall difference can be seen between these groups.

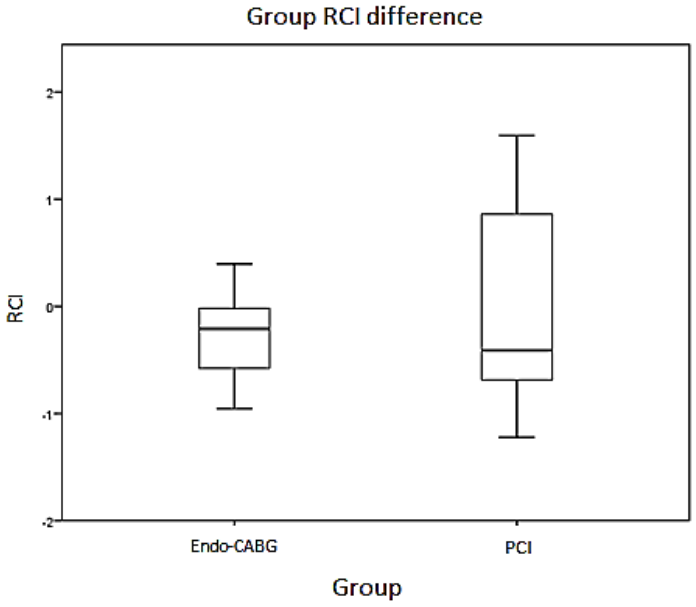


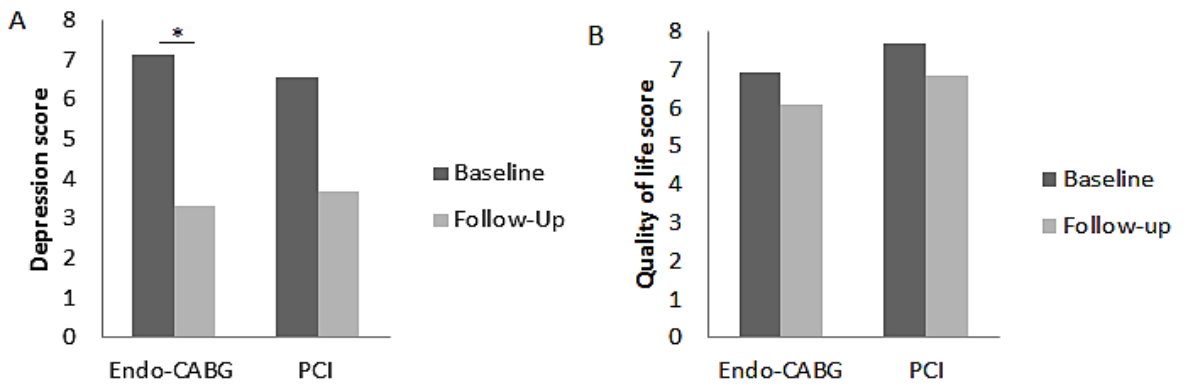
Figure 11: Boxplot output of mean group RCI scores of the different neurocognitive tests.

3.3.4 COMPARISON OF THE QUALITY OF LIFE, FEAR AND DEPRESSION: DIFFERENCES BETWEEN ENDO-CABG AND PCI

At the follow-up point, depression and quality of life are assessed. This can be compared with the baseline score for these factors. Fear before surgery is only tested at the baseline test moment. The difference in fear before surgery between Endo-CABG and PCI subject at the baseline test moment was only significant for the short term fear ($p = 0.013$). The PCI subjects showed a significantly lower short term fear in comparison to the Endo-CABG patients. When looking at long term fear for the consequences in the long run, there was no significant difference between these two groups (0.557).

For the comparison of the quality of life and depression, different factors can be checked. The baseline tests showed no significant difference of quality of life and depression between the Endo-CABG group and the PCI group. First, we will check if at the follow-up test moment the depression between these groups is significantly different. Second, we will compare the mean group differences between follow-up and baseline measurements of the Endo-CABG group and the PCI group.

The difference between the follow-up tests and the baseline tests indicate whether a group is improved or declined in overall depression or quality of life. The difference of these scores will be tested using a Mann-Whitney U test at significance level 5%.



Tests	Endo-CABG		p-value	PCI		p-value
	Baseline	Follow-up		Baseline	Follow-up	
Depression	7.15 (5.52)	3.31 (3.57)	0.05*	6.57 (4.89)	3.71 (4.11)	0.274
Quality of life	6.92 (1.89)	6.08 (1.94)	0.383	7.71 (2.29)	6.86 (2.55)	0.299

*Figure 12: The difference in depression and quality of life scores between baseline and follow-up measurements. A. Difference in depression scores for Endo-CABG and PCI groups. B. Difference in quality of life scores for Endo-CABG and PCI groups. *significant difference at significance level 5%*

In Figure 12 the results of the analysis of the depression and quality data is shown. The depression score difference in the Endo-CABG group show significant differences (p = 0.05). This shows that the depression state of Endo-CABG subjects is significantly decreased when compared to the baseline measurement (Figure 12A). This effect is not seen in the PCI group (p = 0.274). This may be due to the low population number of the PCI group (N = 7).

The quality of life difference shows no significant chances in the different groups (Figure 12B). In both the Endo-CABG group and PCI group no significant decrease can be seen between the baseline and follow-up measurement.

Next we compared the difference between the Endo-CABG and the PCI group. We compared the mean difference between follow-up and baseline for depression and quality of life between these two groups. The mean values were analysed using a Mann-Whitney U test at a significance level of 5%.

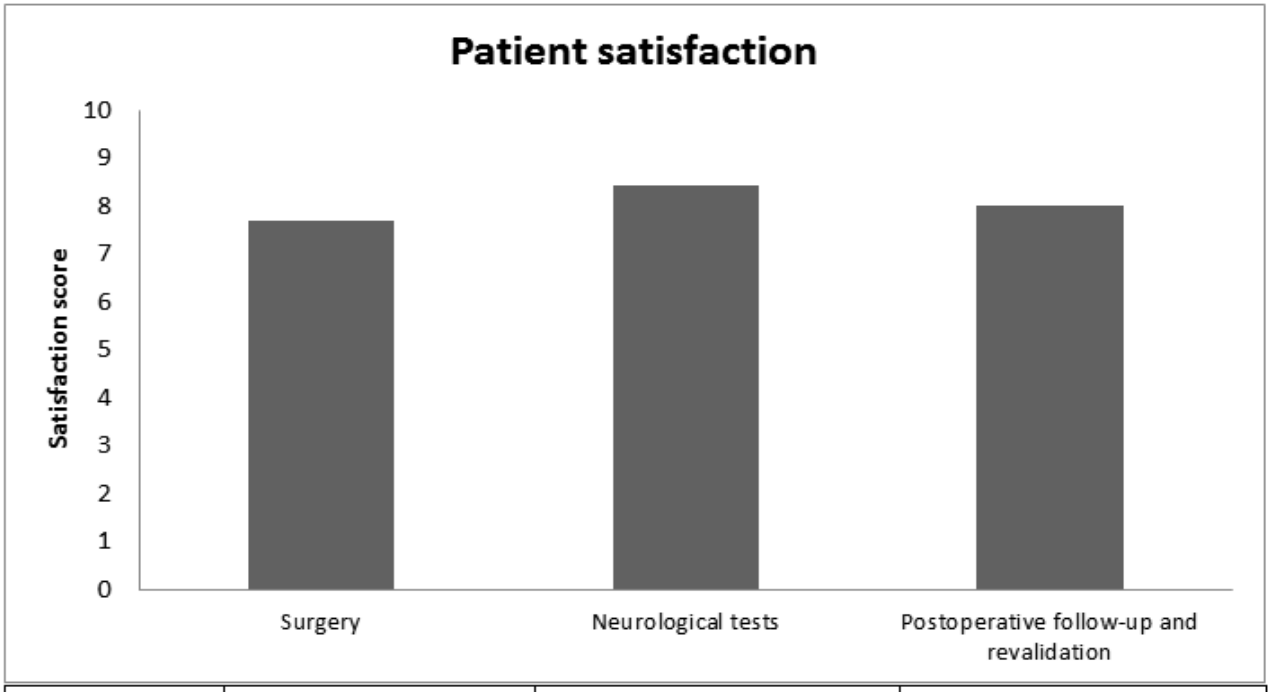
Table 13: Difference in Depression and quality of life between Endo-CABG and PCI group.

Tests	Endo-CABG	PCI	p-value
Depression	-3.85 (5.66)	-2.86 (4.55)	0.603
Quality of life	-0.85 (2.08)	-0.86 (2.12)	0.872

In Table 13 the difference in depression and quality of life between the Endo-CABG and PCI group is shown. No significant differences could be found between the two groups indicating that the mean difference scores is the same for the groups.

3.3.5 PATIENT SATISFACTION AFTER ENDO-CABG SURGERY AND NEUROCOGNITIVE TESTING

At the follow-up measurement patient satisfaction was measured. This was done by conducting a questionnaire containing three questions about different aspects: surgery and postoperative care, the neurological tests and the method of action, and postoperative follow-up and revalidation. Every question delivers a score between 0 and 10.



	Surgery	Neurological tests	Follow-up and revalidation
Satisfaction	7.71 (0.88)	8.43 (0.82)	8 (0.76)

Figure 13: Patients satisfaction after Endo-CABG surgery.

The overall satisfaction of the subjects is high ranging the mean scores between 7.7 and 8.4 (Figure 13). This indicated that patients undergoing Endo-CABG surgery have a good outcome and have good postoperative care. Also neurological testing was appreciated by the test subjects.

4 CONCLUSION

Neurological complications after major cardiac surgery have been a recurrent problem since the first cardiac surgery has been performed. A lot of improvements have been made in the last decade making cardiac surgery less invasive, less expensive (hospitalisation costs), and ultimately reduced the overall mortality in cardiac surgery (2, 3). Still neurological complications are a recurrent problem after cardiac surgery.

In this report we tried to compare two different approaches of the same problem. Historically, coronary artery bypass grafting (CABG) was performed using classic sternotomy (Invasive incision of the sternum) to reach the heart. In the past few years in the Jessa hospital, a new minimal invasive procedure (Endoscopic-CABG) was introduced showing improvement in postoperative survival and quality of life but also showing less mortality. When it comes to neurological complications, not much was known about neurological outcome after Endo-CABG procedures.

In this report preliminary data was shown on the neurological outcome after endoscopic coronary artery bypass grafting (Endo-CABG). Firstly, we tried to prove that the Incidences of neurological complications after surgery were at least similar to the conventional way of CABG surgery (3, 5, 18, 28). In our study preliminary data showed no incidence of delirium (0/24). This would indicate that the outcome of delirium after Endo-CABG is improved compared to conventional CABG procedures (. In conventional CABG a total incidence of delirium of 10-30% postoperatively has been reported in several studies. Because still not all patients have been included in the study this is still a preliminary indication.

Postoperative stroke has been associated to different kinds of cardiac surgery. In our study the number of Endo-CABG patients who suffered from a postoperative stroke (1/24; 4.16%) was similar to the incidences described in several studies about stroke after conventional CABG methods (1-5%). Also for postoperative cognitive dysfunction (POCD) the number of patients suffering from POCD (2/14; 14.3%) was similar to the number of patients suffering from POCD after conventional CABG surgery (20-40%) as indicated in several studies. Although the number of POCD patients after Endo-CABG surgery seems lower compared to this number after conventional CABG, no final conclusion can be made about this because of the small follow-up sample size of the Endo-CABG group (N = 14). Preliminary data tend to show us that Endo-CABG surgery has a better neurological outcome compared to conventional CABG surgery, especially for delirium outcomes and to a lesser extent for POCD outcomes after surgery.

Secondly, in this study we compared two major coronary artery interventions performed at the Jessa Hospital. The preliminary data of the neurological outcome of the above mentioned Endo-CABG surgery

was compared to the neurological outcome of subject who received a percutaneous coronary intervention (PCI). Here no major differences could be found between the two groups. The incidence of postoperative stroke was similar for both groups (endo-CABG = 1/24; PCI = 1/33). The outcome of POCD was also compared between the Endo-CABG and the PCI group. Here no significant differences could be found between the Endo-CABG group (2/14) and the PCI group (2/8). No final conclusion could be made between these two groups because of the small sample sizes at the follow-up point.

Other factors compared between the endo-CABG group and the PCI group were fear, depression and quality of life. Only for short term fear, a significant difference was found between the groups ($p = 0.013$). Short term fear was significantly lower in the PCI group. This can be due to the fact that people still have a common perception about the severity of coronary artery bypass grafting compared to PCI. Depression and quality of life showed similar results between the Endo-CABG and PCI group.

This preliminary report on the neurological outcome after minimal invasive Endo-CABG surgery indicates that this new method of CABG surgery has some advantages in comparison to the conventional CABG surgery method. Delirium and POCD outcomes show differences with the conventional CABG surgery and tend to be similar to the Neurological outcome after PCI interventions. The incidence of stroke after Endo-CABG is indicated to be in the same order as the incidence of stroke after conventional CABG surgery. This is also seen in the PCI group. Despite the major improvements in cardiac surgery the past decades, still neurological complications are recurrent even in the most minimal invasive cardiac interventions. Because this report was only based at preliminary results no major conclusions could be made. There are major indications that the neurological outcome after Endo-CABG surgery tends to be similar to the neurological outcome after PCI interventions.

Further data collection and further research have to point out the real incidence after Endo-CABG surgery and also identify the major risk factors for postoperative neurological complications. This last step could be the key in the understanding of the mechanisms of how neurological complications are caused and if there is a solution to this recurrent problem after cardiac surgery.

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APPENDIX: ANAESTHESIA PROTOCOL FOR ENDO-CABG AT JESSA (BELGIUM)

ANAESTHESIA:

All patients will receive premedication (alprazolam 0.25-0.5mg) one hour before arrival in the operating theatre. Induction of anaesthesia will be performed with intravenous sufentanil (0.2-0.3 µg/kg) and propofol (1-2 mg/kg). Muscle relaxation will be achieved with cisatracurium (0.15-0.2mg/kg). After induction, anaesthesia will be maintained with a continuous infusion of propofol (2-4mg/kg/h) and remifentanil (0.15-0.25µg/kg/min) and supplements with sufentanil (1-2µg/kg) and cisatracurium as required. During cardiopulmonary bypass (CPB), sevoflurane inhalation (0.5-1%) will be used to maintain mean arterial pressure < 80-90 mmHg. Endotracheal intubation will be achieved with a bronchial blocker (EZ-Blocker, Teleflex) or a double lumen endotracheal tube (Mallinckrodt DLT) for single, separate lung ventilation during thoracoscopic harvesting of the internal mammary arteries.

Patients will be routinely monitored with a central venous and arterial line, continuous cardiac output monitoring by pulmonary artery catheter (Vigilance, Edwards Lifesciences) or in a semi-invasive way (FloTrack/Vigileo,Edwards Lifesciences) and cerebral oxygen saturation with near-infrared spectroscopy (Niro 200-SX, Hamamatsu) from pre-induction until completion of surgery. A full dose of heparin (300 IU/kg) will be administered in both groups and activated clotting time (ACT) will be maintained > 400 seconds. Tranexamic acid will be used as an antifibrinolytic agent. At the end of the procedure heparin will be reversed with protamine at a 1:1 equivalent dosage. Use of inotropic support (dobutamine), vasopression (norepinephrine) and vasodilation (milrinone) will be guided using hemodynamic data and transoesophageal echocardiography (TEE). Thorough TEE examination proves to be crucial in the management of patients with multi-vessel disease undergoing Minimal Invasive Cardiac Surgery (MICS) with Minimal invasive Extra-Corporeal Circulation (MiECC) as for preoperative evaluation, cannulation and perioperative management. Patients with severe atherosclerotic disease grade IV or V in the arch or ascending aorta on intraoperative TEE will be excluded from retrograde aortic perfusion and will be switched to central cannulation with antegrade perfusion (right subclavian artery) due to the risk of stroke.

SURGICAL PROCEDURE OF ENDO-CABG:

Insufflation with carbon dioxide (controlled pneumothorax) will be used to ensure adequate visualization of the structures and to provide sufficient space for harvesting both internal mammary arteries during single lung ventilation. Full arterial revascularization will be performed through an

anterolateral thoracotomy (4-5 cm incision). In multi-vessel coronary artery disease, a Y-graft will be created by using the right mammary artery as free graft onto the left mammary artery.

Cardioplegia will consist of single shot antegrade cold (4°C) mixed cardioplegia 3:1 (blood: crystalloid, Fresenius Kabi, Schelle, Belgium) and will be administered through the aortic root vent. Rectal temperature will be strictly maintained at 35.5-36.5°C and blood glucose levels will be controlled with an infusion of short-acting insulin. Warm blood ('hot shot') will be administered by the aortic root before removing the transthoracic clamp (Chitwood).

CARDIOPULMONARY BYPASS (CPB):

CPB in the MiECC group consists of a totally closed phosphorylcholine coated circuit with Revolution centrifugal pump (Sorin S.p.A., Mirandola, Italy), Inspire microporous hollow fibre membrane oxygenator (Sorin S.p.A., Mirandola, Italy) with integrated arterial filter and venous bubble trap (Sorin S.p.A., Mirandola, Italy). The system will be primed with 1000 ml of Plasma-Lyte® A (Baxter International Inc., Deerfield, IL, USA) without heparin. The priming solution will be evacuated out of the circuit and replaced by the patient's blood to minimize haemodilution. Due to this intervention, no heparin will be added to the priming solution. De-priming of arterial and venous lines reduces priming volume to 300 ml. A blood collection bag will be integrated in the circuit, should positioning of the patient be insufficient in coping with excessive volumes. No open reservoir will be present. Cell saver drainage will be used for intra-pericardial bloodshed. Aortic root venting will run via the upper bubble trap to minimize back-bleeding in coronary arteries. Non-pulsatile flow at 1.8-2.4 L/min/m^2 will be maintained with mean arterial pressure between 70-80 mmHg with norepinephrine or sevoflurane. The pH will be managed according to the alpha-stat principle.

POSTOPERATIVE MANAGEMENT:

All patients will be transferred to the intensive care unit (ICU) and will be extubated depending on clinical criteria within 2-6 h after surgery. For postoperative analgesia a continuous infusion of local anaesthetics (ropivacaine 0.2%, 6 ml/h) through a catheter in the intercostal and paravertebral space will be used for 3 days. The catheter will be placed by the surgeon under endoscopic guidance at the end of the procedure and a single shot bolus (ropivacaine 0.5 %, 10 ml) will be administered.

Postoperative analgesia will be further provided with intravenous paracetamol and a continuous infusion of piritramid. Hyperthermia will be strictly avoided and blood glucose levels will be controlled with an infusion of short-acting insulin.

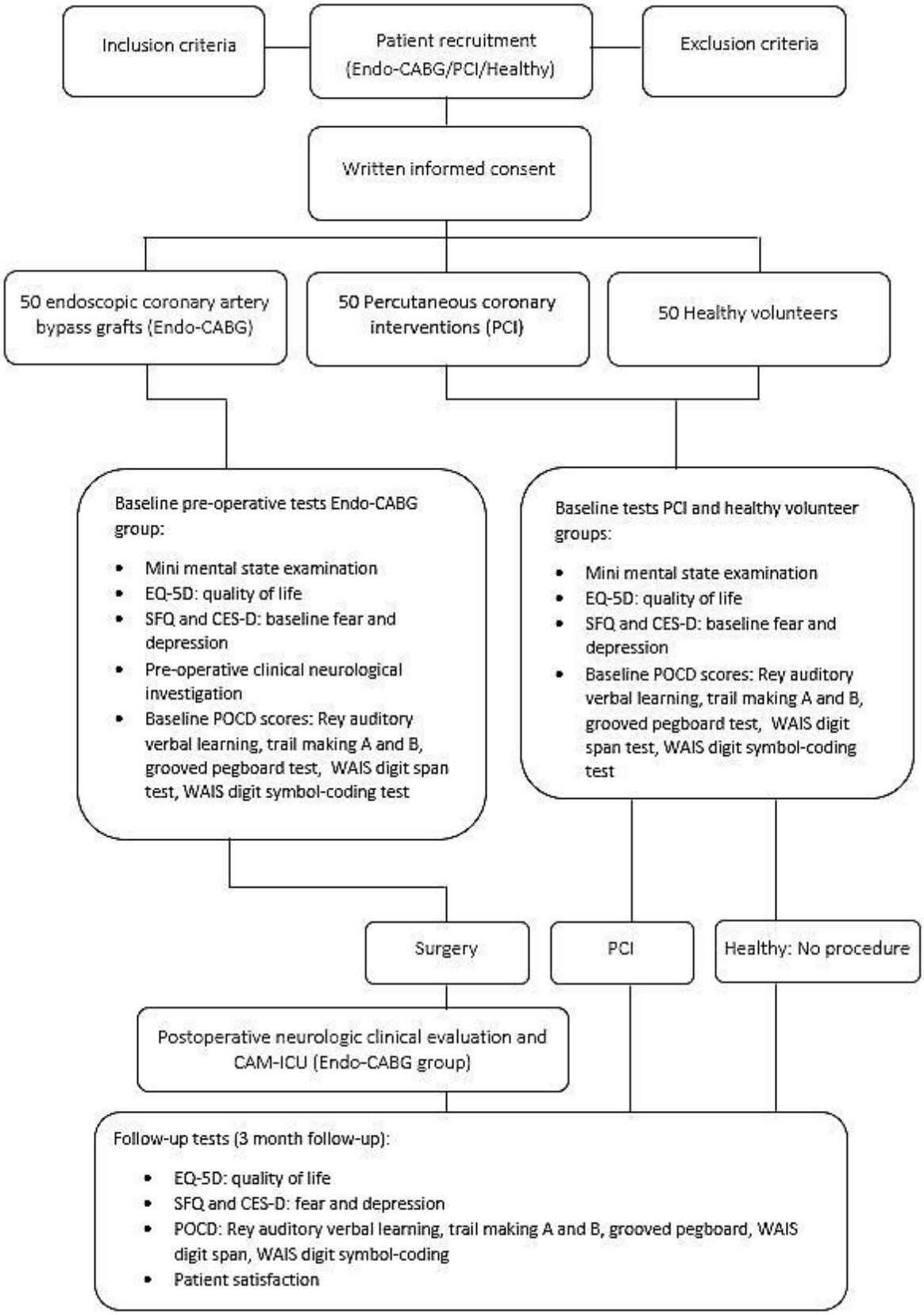
On the ICU, a prevention program on postoperative delirium was implemented, which consists of minimal sedation, avoidance of benzodiazepines and early mobilization. The nursing staff tries to create a healing environment based on a patient-centered approach with interventions for re-orientation, improvement of sensory input (visual and hearing aids) and non-pharmacological sleep enhancement strategies (noise and light reduction, minimal nursing interventions at night).

SUPPLEMENTAL DATA

Table S1: Eligibility criteria inclusion NOMICS study.

Inclusion criteria	Exclusion criteria
- Minimum age of 18 years - Elective Endo-CABG procedure (group 1) - Elective PCI procedure (group 2) - Healthy volunteers (group 3)	- Medical history of: ➢ Postoperative cognitive dysfunction, delirium or cerebrovascular accident ➢ Symptomatic carotid artery disease ➢ Dementia (score MMSE < 20/30) ➢ Renal dysfunction: glomerular filtration rate (GFR) < 30 ml/min ➢ Hepatic dysfunction: serum glutamic oxaloacetic transaminase (SGOT)/ aspartate aminotransferase (AST), or serum glutamic-pyruvic transaminase (SGPT)/ alanine aminotransferase (ALT), more than three times higher than normal limits - History of drug and/or alcohol abuse - Language barrier or incapability to communicate - Physical condition making participation impossible - Participation in other clinical trials of a drug or medical instrument - Surgical revision or intra-operative major cardiac event (Endo-CABG group) - Conversion to cardiac surgery or major intra-operative adverse event (PCI group)

Figure S1: Protocol NOMICS study



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The NOMICS study: The neurological outcome after minimal invasive Endoscopic coronary artery bypass grafting (Endo-CABG)

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Voor akkoord,

Vaqueriza, Fidel

Datum: **7/06/2017**