



PERTTI LOPONEN

Health Related Quality of Life
after Invasive Treatment
of Coronary Artery Disease



ACADEMIC DISSERTATION

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the Faculty of Medicine of the University of Tampere,
for public discussion in the Small Auditorium of Building B,
Medical School of the University of Tampere,
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“Not just the absence of death but life with the vibrant quality of life that we associate with the vigor of youth” (Elkington 1966).

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ABSTRACT

Coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) are the two invasive options for the treatment of coronary artery disease (CAD). Outcome after invasive treatment of CAD is traditionally assessed in terms of major adverse events i.e. in-hospital mortality, cardiovascular complications and long-term survival. These endpoints form the basis in follow-up studies and enable us to make comparisons between treatment modalities in randomized trials. However, the afore-mentioned indicators do not explain how individual patients feel about their lives after coronary artery intervention. The emphasis has subsequently been on assessing outcome also in terms of patients' perception of changes in their state of health over time. Patients are interested in their quality of life following an intervention and they may appreciate this endpoint actually more than clinicians do. Patient-centred outcomes may have value both for risk assessment when selecting treatment and as an outcome measure. Moreover, the highly respected guidelines for invasive treatments of CAD suggest that improvement in quality of life is a primary indication for treatment options.

The aims of the present study were to evaluate changes in health related quality of life (HRQoL) in an original study population consisting of 1,330 patients with suspected CAD. They were referred for invasive examination and asked to participate voluntarily in a survey examining changes in HRQoL after possible invasive treatment during a follow-up of 36 months. The 15D generic measure was used to evaluate HRQoL. Baseline status of HRQoL was assessed before patients underwent angiography of the coronary arteries. Patient groups for analysis were formed according to the findings of angiograms and the decision regarding each treatment option based on a clinical decision-making. Thus the survey was not randomized. Changes in HRQoL were followed prospectively and patients were re-examined three times, at 6, 18 and 36 months after the invasive intervention.

The original study population for Studies I, II and III was 302 patients undergoing CABG. In Study I patients were followed up 18 months and changes in HRQoL were assessed between males and females and in three age groups, i.e. patients under 65 years, patients 65–74 years and patients over 75 years of age. Study II aimed to evaluate the effect of perioperative delirium after CABG on HRQoL. In Study III the aim was to test the capacity of the risk-scoring system EuroSCORE in predicting postoperative HRQoL in a long-term follow-up. Study IV included a non-randomized series of patients with chronic stable CAD, of whom 240 underwent CABG and 224 PCI. The HRQoL as well as the perceived physical performance status of these groups was evaluated during a follow-up of 36 months. In Study V invasive reinterventions were examined between 302 CABG patients and 360 PCI patients in a follow-up of 36 months. The preoperative HRQoL of the CABG patients was compared with that of an age- and gender-matched reference population. The perceived HRQoL of patients with chronic stable CAD was similarly compared to the HRQoL of a reference population at 36 months after treatment.

Complete data on HRQoL was retrieved in 96.3% (I), 92.3% (II, III) and 93.4% (IV) of surviving CABG patients and in 94.9% (IV) of surviving PCI patients.

Patients with CAD had basically significantly poorer HRQoL than the reference population (I). Patients also did not perceive a level of HRQoL equal to that of the reference population 36 months after treatment but remained significantly poorer (IV).

HRQoL demonstrated a two-sloped change as a function of time for both CABG and PCI patient groups after invasive treatment. Initial improvement during the first six months after intervention was followed in any case by an equalization and impairment. The same kind of trajectory was seen in both genders and in all mentioned age groups (I). The finding was similar also between the EuroSCORE risk groups (IV).

Both CABG and PCI patients achieved a statistically significant improvement in their HRQoL at six months after the intervention (I, IV). In CABG patients HRQoL remained at a higher level than before the surgery for 18 months but at 36 months the perceived HRQoL corresponded to the baseline level (I, IV). The process was similar in both genders. Related to age only patients <65 years retained a significantly higher level of HRQoL throughout 18 months in comparison to preoperative state. In patients over 75 years the decline from 6 months onwards was steeper than in the other age groups and statistically HRQoL in this age group ended at the initial level (I). One of the 15 dimensions of the 15D measure, breathing, improved in all subgroups indicating as such the best relief from angina. In the present “real-world” material CABG patients achieved equal level of HRQoL compared with PCI patients

despite a more demanding and risky procedure for CAD treatment (IV). PCI patients were also at significantly higher risk regarding for repeated interventions, angiography, repeat PCI or CABG when compared to CABG patients during follow-up of 36 months (IV, V).

CABG patients achieved even better recovery of physical performance as long as 36 months after the intervention compared to the PCI patients. A total of 85.9% of the CABG patients and 67.5% of the PCI patients improved receiving at least one step lower NYHA class than before treatment ($p < 0.001$) by 36 months. Moreover, 68.3% of the CABG patients and 58.3% of the PCI patients were asymptomatic in their normal lives after 3 years ($p = 0.022$). Clinically relevant improvement was more frequent in the CABG patient group between 0–6 months (48.9% vs. 36.6%, $p = 0.008$) as well as between 0–36 months (39.8% vs. 27.6%, $p = 0.010$ respectively) (IV). Perioperative complications such as delirium worsened the perceived HRQoL and also had a negative effect on the use of resources as well as on the survival of this patient group (II).

The EuroSCORE risk definition measure predicted not only morbidity after CABG but also HRQoL. The best cut-off value of additive EuroSCORE in predicting improved HRQoL was 3. However, the accuracy of the value of the risk assessment system in estimating the postoperative HRQoL of CABG patients was quite far from the ideal in ROC analysis (III).

In conclusion, CABG and PCI improve overall HRQoL for a wide range of CAD patients in short follow-up, especially in younger ages. Despite initially more serious preoperative state CABG patients achieve equal improvement of HRQoL when compared with PCI patients. In long term CABG patients may obtain better relief from symptoms and a better state of physical performance without the significant burden of repeated invasive interventions. HRQoL assessed by a generic measure cannot be the only factor to determine outcome after invasive treatment of CAD but has to be placed in the context of the overall situation.

TIIVISTELMÄ (ABSTRACT IN FINNISH)

Sepelvaltimoiden ohitusleikkaus ja pallolaajennus, joko sellaisenaan tai yhdistettynä suonen sisäisen verkkotuen asettamiseen, ovat sepelvaltimotaudin kajoavia hoitomuotoja. Sepelvaltimoihin kohdistuvan hoidon tuloksia on perinteisesti arvioitu tutkimalla suuria päätetapahtumia, kuten sairaalakuolleisuutta, sydän- ja verisuoniperäisiä komplikaatioita sekä pitkän ajan eloonjäämistä, joita yleisesti käytetään satunnaistetuissa tutkimuksissa vertailtaessa hoitomuotoja keskenään. Näillä ilmaisimilla emme kuitenkaan saa selville, kuinka yksittäinen potilas kokee elämänsä sepelvaltimohoidon jälkeen. Potilaat ovat kiinnostuneita saavutettavissa olevasta elämänlaadusta ja he arvostavat tätä päätetapahtumaa jopa enemmän kuin heitä hoitavat klinikot. Potilaslähtöisellä arvioinnilla voi olla merkitystä valittaessa hoitoa sekä arvioitaessa hoidon tuloksellisuutta. Arvostettuihin sepelvaltimotaudin kajoavasta hoidosta annettuihin ohjeistuksiin on kirjattu että elämänlaadun paraneminen on yksi kajoavan hoidon primäärisistä aiheista.

Tutkimuksen tarkoituksena oli selvittää elämänlaadun muuttumista potilasjoukossa, joka koostui 1330 epäillyn sepelvaltimotaudin takia kajoavaan tutkimukseen (sepelvaltimoiden varjoainekuvaus) lähetetystä potilaasta. Ennen varjoainekuvausta potilaita pyydettiin vapaaehtoisesti osallistumaan tutkimukseen, jossa heidän elämänlaatunsa muuttumista tulnaisiin seuraamaan kyselyin 6, 18 ja 36 kuukautta tehdyn varjoainekuvauksen ja sen perusteella mahdollisesti suoritettujen ohitusleikkauksen tai pallolaajennuksen jälkeen. Elämänlaadun mittaus tapahtui 15D-mittaria käyttäen. Seurattavat potilasryhmät, ohitusleikkauspotilaat tai pallolaajennuspotilaat, muotoutuivat angiografian jälkeen, kun sen antaman tuloksen perusteella potilaalle tehtiin mahdollisesti ohitusleikkaus tai pallolaajennus. Tutkimus ei ollut satunnaistettu.

Osatöissä I–III tutkittava potilasjoukko koostui 302 ohitusleikkauspotilaasta. Tutkimuksessa I potilaiden elämänlaatua seurattiin 18 kuukauden ajan miehillä, naisilla sekä kolmessa ikäryhmässä (alle 65-vuotiaat, 65–74-vuotiaat ja yli 75-vuo-

tiat). Osatyössä II tutkittiin ohitusleikkaukseen liittyneen ohimenevän sekavuuden (delirium) vaikutusta elämänlaatuun 36 kk:n seuranta-ajalla. Osatyö III pyrki arvioimaan yleisesti käytössä olevan, leikkauskuolleisuusriskiä arvioivan mittarin (EuroSCORE) kykyä arvioida saavutettavaa elämänlaatua 36 kk aikana ohitusleikkauksen jälkeen. Osatyössä IV tutkittiin kroonisen, hoitohetkellä tasapainossa olevan sepelvaltimotaudin kajoavan hoidon (ohitusleikkaus tai pallolaajennus) jälkeistä elämänlaatua ja sepelvaltimotaudin aiheuttaman oireen häviämistä kahdessa satunnaistamattomassa potilasryhmässä pitkällä seuranta-ajalla. Osatyössä V selvitettiin uusien kajoavien hoitojen tarvetta ensimmäisen pallolaajennuksen tai ensimmäisen ohitusleikkauksen jälkeen 36 kk:n aikana.

Täydelliset elämänlaatua koskevat seurantatiedot saatiin 95.3%:lta (I), 92.3%:lta (II, III) ja 93.4%:lta (IV) elossa olevista ohitusleikkauspotilaista ja 94.9 %:lta (IV) pallolaajennuspotilaista.

Sepelvaltimotautia sairastavien potilaiden elämänlaatu oli ennen tehtyä toimenpidettä huonompi kuin vertailuväestössä (I). Myös 36 kuukauden seuranta-ajan jälkeen potilaiden elämänlaatu jäi merkitsevästi huonommaksi kuin vertailuaineistossa (IV).

Terveysteen liittyvän elämänlaadun muutos tapahtui kaksivaiheisesti seurantajakson aikana sekä ohitusleikkaus- että pallolaajennuspotilailla. Toipumisen alkuvaiheen, kuuden kuukauden aikana tapahtunutta paranemista seurasi elämänlaadun tasapainottuminen ja huonontuminen. Tämä muutos tapahtui molemilla sukupuolilla ja eri ikäryhmissä (I). Muutos oli samanlainen myös EuroSCORE-riskiryhmissä.

Sekä ohitusleikkaus- että pallolaajennuspotilaiden terveyteen liittyvä elämänlaatu parani tilastollisesti merkitsevästi kuuden kuukauden kuluessa toimenpiteen jälkeen (I, IV). Ohitusleikkauspotilailla elämänlaatu oli lähtötasoa merkitsevästi korkeampi 18 kuukauden kohdalla mutta 36 kuukauden kuluttua leikkauksesta taso vastasi ennen leikkausta havaittua (I, IV). Tulos oli sama kummankin sukupuolen kohdalla. Alle 65-vuotiaiden terveyteen liittyvä elämänlaatu oli 18 kuukauden kuluttua merkitsevästi parempi kuin lähtötilanteessa. Yli 75-vuotiaiden elämänlaadun tasossa tapahtunut huononeminen kuuden ensimmäisen kuukauden paranemisen jälkeen oli jopa jyrkempi kuin muissa ikäryhmissä ja nämä potilaat päätyivät tilastollisesti lähtötasolleen (I). 15D-mittarin ulottuvuuksista koettu paraneminen hengittämisessä oli havaittavissa kaikissa alaryhmissä: tämä löydös vastannee parhaiten angina-oireen häviämistä. Ohitusleikkauspotilaiden terveyteen liittyvä elämänlaatu parani samalla tavalla kuin pallolaajennuspotilailla huolimatta alunpitäen vaativammasta ja riskialttiimmasta toimenpiteestä tämän ajan tyyppillisessä

potilasmateriaalissa. Pallolaajennuspotilaille tehtiin lisäksi merkittävästi enemmän kajoavia uusintatoimenpiteitä 36 kuukauden seurantajakson aikana (IV, V).

Ohitusleikkauspotilaiden fyysinen suorituskyky korjaantui paremmin ja se myös pysyi parempana koko seurannan ajan. Kolmen vuoden kuluttua tehdystä toimenpiteestä 85.9% ohitusleikkauspotilaista ja 67.5% pallolaajennuspotilaista oli parantunut ainakin yhden luokan verran kun mittarina käytettiin NYHA-luokitusta ($p < 0.001$). Lisäksi 68.3% ohitusleikkauspotilaista ja 58.3% pallolaajennuspotilaista oli oireettomia seurannan päättyessä ($p = 0.022$). Kliinisesti merkittävä terveyteen liittyvän elämänlaadun paranemista tapahtui enemmän ohitusleikkauspotilailla verrattuna pallolaajennuspotilaisiin 6 kuukauden kohdalla (48.9% ja 36.6%, $p = 0.008$) ja 36 kuukauteen mennessä (39.8% ja 27.6%, $p = 0.010$) (IV). Leikkaukseen liittyvänä komplikaationa delirium huononsi saavutettua leikkauksen jälkeistä elämänlaatua ja aiheutti myös resurssien lisäkättöä ja alensi eloonjäämisenustetta (II).

EuroSCORE-riskiluokituksen todettiin ennustavan paitsi ohitusleikkaukseen liittyvää sairastuvuutta myös terveyteen liittyvää elämänlaatua. Riskipistemäärä korkeintaan 3 ennusti paranevaa terveyteen liittyvää elämänlaatua. ROC-analyyseissä tämän testin tarkkuus ei kuitenkaan ollut ihanteellinen (III).

Yhteenveto: tutkimuksen perusteella voitiin todeta, että terveyteen liittyvä elämänlaatu parani sekä ohitusleikkaus- että pallolaajennuspotilailla lyhyellä seuranta-ajalla ja erityisesti paraneminen havaittiin nuoremmista ikäryhmissä. Vaikka ohitusleikkauspotilaat ovat huomattavasti vaativamman toimenpiteen kohteena, he saavuttavat vähintään saman terveyteen liittyvän elämänlaadun paranemisen kuin pallolaajennuksen läpikäyneet potilaat. Pitkällä tarkastelujaksolla ohitusleikkauspotilaat ovat oireettomampia, heidän fyysinen suorituskykynsä on parempi ja heitä rasittaa merkittävästi vähäisempi riski joutua uuteen kajoavaan tutkimukseen tai hoitoon. Geneerisellä mittarilla mitattua elämänlaatua ei kuitenkaan voi pitää ainoana menetelmänä arvioitaessa sepelvaltimotaudin kajoavan hoidon tuloksia, vaan se on asetettava yleistilanteeseen nähden oikeaan asemaan.

ABBREVIATIONS

ACC	American College of Cardiology
AHA	American Heart Association
AF	atrial fibrillation
AMI	acute myocardial infarction
ANOVA	analysis of variance
AP	angina pectoris
ASA	American Society of Anaesthesiologists
ASO	arteriosclerosis obliterans
AUC	area under the receiver operating characteristic curve
BMS	bare metal stent
CAD	coronary artery disease
CABG	coronary artery bypass grafting
CCS	Canadian Cardiovascular Society
CHF	congestive heart failure
CI	confidence interval
CKMBm	creatinine kinase cardiac isoenzyme mass
COPD	chronic obstructive pulmonary disease
CPB	cardiopulmonary bypass
CT	computed tomography scan
CVD	cerebral vascular disease
DES	drug-eluting stent
ECC	extracorporeal circulation
ECG	electrocardiogram
EF	ejection fraction
HR	hazard ratio

HRQoL	health related quality of life
IABP	intra-aortic balloon pump
ICU	intensive care unit
ITA	internal thoracic artery
LAD	left anterior descending coronary artery
LCX	left circumflex coronary artery
LMCA	left main coronary artery
LOS	low output syndrome
LVEF	left ventricular ejection fraction
NYHA	New York Heart Association
NHP	Nottingham Health Profile
MACE	major adverse cardiovascular event
MACCE	major adverse cardiovascular or cerebral vascular event
MCS	mental component summary
MI	myocardial infarction
MIDCAB	minimally invasive direct bypass grafting
MVD	multivessel disease
OPCAB	off pump coronary artery bypass
OR	odds ratio
PCI	percutaneous coronary intervention
PCS	physical component summary
PTCA	percutaneous transluminal coronary angioplasty
RCA	right coronary artery
ROC	receiver operating characteristic
RR	relative risk
SPSS	Statistical Package for the Social Sciences
STS	Society of Thoracic Surgeons
TIA	transient ischemic attack
UAP	unstable angina pectoris
VD	vessel disease
WHO	World Health Organization

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following five original papers referred to in the text by their Roman numerals I–V.

- I Pertti Loponen, Michael Luther, Jan-Ola Wistbacka, Kari Korpilahti, Jari Laurikka, Harri Sintonen, Heini Huhtala, Matti R Tarkka. Quality of life during 18 months after coronary artery bypass grafting. *Eur J Cardiothorac Surg* 2007; 32: 77–82.
- II Pertti Loponen, Michael Luther, Jan-Ola Wistbacka, Juha Nissinen, Harri Sintonen, Heini Huhtala, Matti R Tarkka. Postoperative delirium and health related quality of life after coronary artery bypass grafting. *Scand Cardiovasc J* 2008; 42: 337–344.
- III Pertti Loponen, Michael Luther, Juha Nissinen, Jan-Ola Wistbacka, Fausto Biancari, Jari Laurikka, Harri Sintonen, Matti R Tarkka. EuroSCORE predicts health-related quality of life after coronary artery bypass grafting. *Interact Cardiovasc Thorac Surg* 2008; 7: 564–568.
- IV Pertti Loponen, Michael Luther, Kari Korpilahti, Jan-Ola Wistbacka, Heini Huhtala, Jari Laurikka, Matti R Tarkka. HRQoL after coronary artery bypass grafting and percutaneous coronary intervention for stable angina. *Scand Cardiovasc J* 2009; 43: 94–99.
- V Pertti Loponen, Kari Korpilahti, Michael Luther, Heini Huhtala, Matti R Tarkka. Repeat intervention after invasive treatment of coronary arteries. *Eur J Cardiothorac Surg* 2009; 35: 43–47.

1 INTRODUCTION

Coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) have a long history as invasive options for treating patients with coronary artery disease (CAD). CABG was first performed in 1964 (Favaloro 1968, Garret et al. 1973) and it has been firmly established since the 1960's as an important alternative method in the care of patients suffering from angina pectoris resistant to medical treatment. The development of extracorporeal circulation (ECC) was epochal. Less invasive methods, i.e. minimally invasive direct coronary bypass (MIDCAB) and off-pump coronary bypass (OPCAB) have been novel innovations aiming to make bypass grafting procedure less burdensome for the patient and to make it safer in cases with certain co-morbidities. Percutaneous transluminal coronary angioplasty (PTCA), for one, was launched 1979 (Grüntzig et al. 1979) as an angio-radiological therapeutic procedure to treat the stenotic (narrowed) coronary arteries of the heart found in CAD patients. Technical progress has been still more intense in this field and introduced devices, i.e. stents (Sigwart et al. 1987) intended to improve not only long-term patency of treated lesions but also the prognosis of patients. Both methods, CABG and PCI, are accepted for treatment in chronic stable CAD but also in acute coronary events.

The interventional efficacy and relative benefits have been compared in several randomized and observational studies (BARI Investigators 1997, Serruys et al. 2001, SoS Investigators 2002, Borkon et al. 2002, Serruys et al. 2005). Mortality and severe morbidity after CABG have decreased in recent decades in spite of the fact that patients are now older and have a higher degree of co-morbidity than 10 to 20 years ago (Ferguson et al. 2002, Falcoz et al. 2006) When selecting the mode of treatment for coronary revascularization, the technical outcome may not be the only consideration. Post procedural health status, including symptoms, functionality and health related quality of life (HRQoL) are also important endpoints (Chocron et al. 1996, Sjöland et al. 1997, Hunt et al. 2000, Järvinen et al. 2003, Kattainen et al. 2005).

Particularly in older age, when the life expectancy is naturally limited, HRQoL has emerged as an increasingly important indication for surgery (Fruitman et al. 1999, Conaway et al. 2003, Markou et al. 2008, Jokinen et al. 2008).

Both CABG (Caine et al. 1991, Chocron et al. 1996, Hunt et al. 2000, Falcoz et al. 2003, Järvinen et al. 2003, Rumsfeld et al. 2004, Kattainen et al. 2005) and PTCA/PCI (Pocock et al. 1996, Brorsson et al. 2001, Kattainen et al. 2005, Lukkarinen et al. 2006) have been demonstrated to improve HRQoL at least in selected patient groups. On the other hand, certain stabilization and even impairment has been proved in HRQoL during a long-term follow-up (Sjöland et al. 1997, Yun et al. 1999, Herlitz et al. 2003, Falcoz et al. 2006). Several preoperative risk factors and co-morbidities certainly influence post-procedural outcome, including HRQoL (Rumsfeld et al. 2004). The same concerns the perioperative complications, inevitably inherent in invasive treatment of CAD. Cardiac surgeons have alternative instruments, i.e. the Cleveland score (Parsonnet et al. 1989) and the EuroSCORE (Nashef et al. 1999), in predicting risk of mortality after CABG. However, cardiologists and cardiac surgeons do not have instruments to assume post-interventional HRQoL on the grounds of preoperative factors or co-morbidities.

The present series of studies was designed to investigate HRQoL of patients undergoing CABG or PCI in short (six months), mid-term (18 months) and in long-term (36 months) follow-up. Moreover, the aim of the study was to evaluate possible differences in post-procedural HRQoL between the two genders and in different age groups. We also wanted to test the ability of a risk evaluating measure, the EuroSCORE, to predict HRQoL after CABG. As delirium is one of the most frustrating postoperative adverse events in cardiac surgery, we aimed to assess its effect on postoperative HRQoL. We studied also changes in HRQoL and in physical performance of patients with chronic stable CAD after either CABG or PCI, as well as necessity of repeat interventions related to aforementioned treatments.

2 REVIEW OF THE LITERATURE

2.1 Quality of life

2.1.1 Mainstream definition

For ordinary use quality of life (QoL) is defined as follows: “Quality of life (QoL) is the degree of well-being felt by an individual or group of people. It is not a concrete thing and so cannot be measured directly. It consists of two components: physical and psychological. The physical aspect includes such things as health, diet, and protection against pain and disease. The psychological aspect includes stress, worry, pleasure and other positive or negative emotional states. It is virtually impossible to predict the quality of life of a specific individual, since the combination of attributes that leads one individual to be content is rarely the same for another individual. However, one can assume with some confidence that the higher average level of diet, shelter, safety, as well as freedoms and rights a general population has, the better overall quality of life it experiences” (Wikipedia, the free Encyclopaedia 2008; http://en.wikipedia.org/wiki/Quality_of_life).

2.1.2 Official WHO definition

The World Health Organization (WHO) defines quality of life as “the individual’s perception of his/her position in life, within the cultural context and the values in which he/she lives, as well as relation to his/her objectives, expectations, standards and concerns”. Thus, according to WHO, QoL consists of physical, mental and social well-being. This is also the basis on which the measures used to evaluate QoL may rely (WHOQOL Group 1998).

2.1.3 Health related quality of life (HRQoL)

HRQoL is an individual's perception of his/her symptoms, well-being and physical and mental functional capacity (Herlitz et al. 1999). Conceptually the term is based on the definition of the WHO for health. Compared to the term QoL, HRQoL is a more comprehensive and more complex concept. Several different fields of human life influence it. Although wide agreement prevailed over the multidimensional construct of HRQoL, there was no clear agreement in the 1980s the dimensions on which HRQoL should be assessed (Kaplan 1988). According to Blumenthal et al. (1994) and Jenkins et al. (1994) major domains with regard to QoL assessment were physical functioning, emotional status, cognitive performance, social functioning, general perceptions of health and well-being, and disease-specific symptoms. In the context of clinical interventions, it might be advisable to qualify the term QoL and use the expression "health related quality of life" instead (Kind 2001).

Wilson and Cleary (1995) introduced a useful organizing framework for categorizing predictors of HRQoL. They distinguished psychological and biological factors, symptoms (including emotional and cognitive variables), individual characteristics, such as gender or age, and environmental characteristics, such as provision of services. All these elements comprise an entity, which is called overall quality of life (Figure 1).

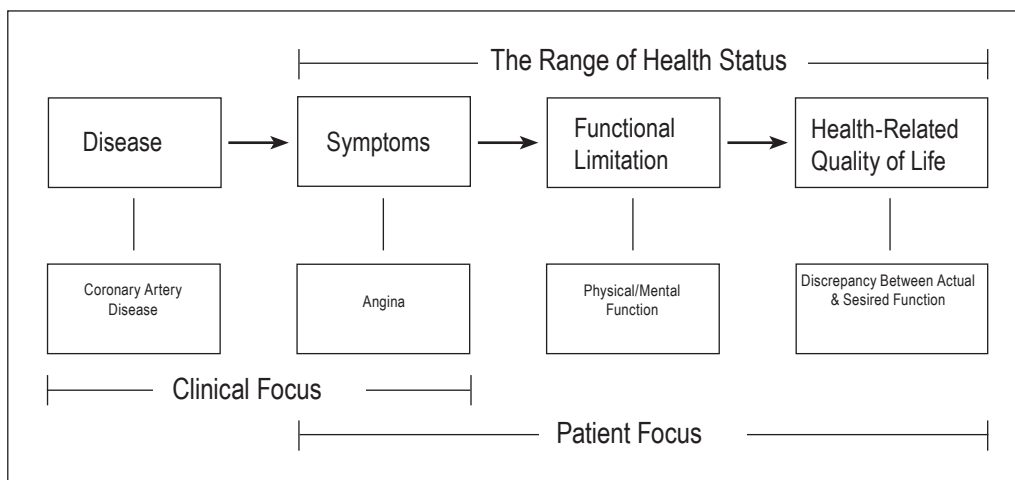


FIGURE 1. The range of health status: symptoms, function, and quality of life. Figure is modified from Spertus et al. 2002 and Wilson and Cleary 1995.

2.1.4 Health status

In pre-interventional discussion patients and clinicians may use a more popular expression “health status” when characterizing the impact of a disease, i.e. CAD on the present condition. Health status is the impact of disease on patient function as reported by the patient (Rumsfeld 2002).

From the patient’s point of view the manifestation of the disease includes symptoms, functional limitation and effects on quality of life. In the context of CAD a patient typically has symptoms of angina. Symptoms cause functional limitation, which may be both physical and mental. Functional limitation forms the outcome, which is the object of our research. Herein HRQoL is the discrepancy between actual and desired function (Figure 2).

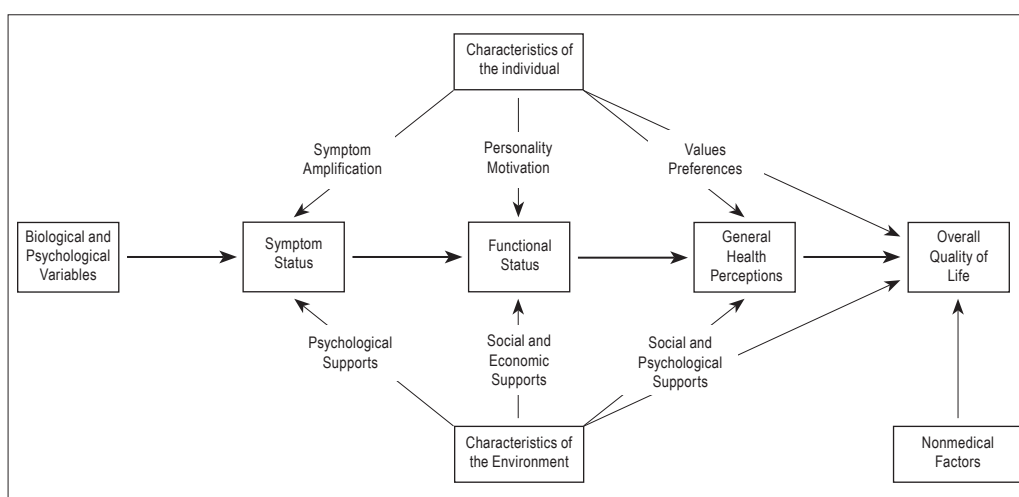


FIGURE 2. Overall QoL from the patient’s point of view. Figure is modified from Wilson and Cleary 1995.

As a clinician easily focuses on the basic illness and its symptoms, a patient’s focus is wider and includes not only the symptoms of the underlying disease but also its effects on function together with its consequences for actual QoL. The range of health status consists of the same dimensions as mentioned before. Patient report is the most essential because a clinician may not estimate the health status of patients accurately. This may lead to a large discrepancy between patient-rated and physician-rated symptom burden and functional limitation (Calkins et al. 1991).

There may also be a poor correlation between objective test results, e.g., the severity of CAD in coronary angiography and patient-reported health status (Nelson

et al. 1991). Therefore, to be more patient-oriented standardized surveys should be used to measure the complete spectrum of health status (Rumsfeld 2002).

2.1.5 Measuring and weight of HRQoL outcomes

Since the 1980's researchers have proposed several instruments to measure HRQoL. The most used measures in assessing HRQoL after treatments for CAD are the Nottingham Health Profile (NHP) (Hunt et al. 1981, Falcoz et al. 2002), the Medical Outcomes Study Short Form (SF-36) (Ware and Sherbourne 1992, Kiebzak et al. 2002), the RAND 36-Item Health Survey (RAND-36) (Hays et al. 1993, Hays et al. 2001), the EuroQol (EQ-5D) (The EuroQol Group 1990, Brooks 1996) and the 15D (Sintonen 1981, Sintonen and Pekurinen 1989). These measures have in common that it is the patient's perception, not the practitioner's view of the technical success that is being measured. They include inquiries that will reveal the impact on life of any anticipated negative effects or incomplete success of the treatment under evaluation. Such measures entail numerous challenges. The measures used should be in the form of self-completed questionnaires, which are sufficiently easy to use, but at the same time reliable and reproducible. The instrument should also be adequately sensitive to change and discriminate within the range of reported experience of the group of patients under investigation.

Health status measurements may be suspected not attaching enough weight to examining the outcome after specified interventions. Clinicians may have the perception that health status measurements are 'soft' or not as scientific as physiological measures. However, instruments testing HRQoL have been developed applying sound scientific principles. They have been subjected to extensive validity and reliability testing and they are highly reproducible. They are based on large patient surveys. Instrument users have given feedback, and factor analyses of empirical data have been produced from various patient groups. From this material the instruments have been revised into a useful form (Rumsfeld 2002).

2.1.6 Outcome measurement of invasive treatment of CAD

Outcome after invasive treatment for CAD is assessed in terms of major adverse cardiovascular events (MACE), i.e. in-hospital mortality, cardiovascular complications and long-term survival. However, outcome cannot be assessed solely in objective terms, as such indicators do not explain how people perceive

and experience their own lives. The emphasis has been subsequently on assessing outcome also in terms of patients' perception of changes in their state of health over time and how this affects their lives – assessing the HRQoL (Gill et al. 1994, Duits et al. 1997). Patients are interested in their quality of life after an intervention and they may appreciate this endpoint actually more than clinicians do. This has led clinicians and researchers to quantify the impact of specific interventions (Spertus et al. 2002). Patient-centred outcomes are of value both for risk assessment and as an outcome measure (Koch et al. 2008). Moreover, the ACC/AHA guidelines for CABG surgery suggest that improvement in quality of life is a primary indication for CABG surgery (Eagle et al. 1999, Eagle et al. 2004).

2.2 A brief summary of the evolution of CABG and PCI as options for myocardial revascularization

CABG was introduced in 1964 to treat CAD (Favaloro 1968, Garret et al. 1973). Since the first attempt CABG has developed into one of the commonest surgical procedures throughout the world. Surgical and perfusion techniques have advanced abundantly. The procedure has become almost infallible and has substantially reduced mortality among patients undergoing cardiac surgery (Ivanov et al. 1998). Important key points have also been the implementation of arterial bypass conduits and launching minimally invasive (MIDCAB) and off-pump coronary artery surgery (OPCAB) alongside conventional CABG with cardiopulmonary bypass (CPB).

The first CABG in Finland was performed in 1970. The number of annual operations increased progressively from the 1980s onwards and peaked in the middle of the 1990s with 4,577 procedures performed in 1996. However, a decline followed and in recent years the rate of annual CABG procedures has stabilized to a level of 3,700–3,800 operations performed in five university hospitals, in one central hospital and in one private hospital (Statistics of the Finnish Heart Association: http://www.sydanliitto.fi/en_GB/).

PTCA was introduced in 1977 as a technique for the treatment of proximal non-calcified, concentric lesions in a single coronary artery (Grüntzig 1978, Grüntzig et al. 1979). With improvements in equipment and techniques, the use of PTCA expanded to more complex lesions and also to patients with MVD. Palmaz first introduced the use of balloon-mounted tubes in 1985 and 1986, where the first human coronary stents after PTCA was deployed (Sigwart et al. 1987). During the 2000s PCI has progressed in using drug-eluting stents in order to prevent one of the most frustrating adverse outcomes after PCI, in-stent restenosis.

In Finland the first PTCA procedures were performed in 1986. From the second half of the 1990s onwards the number of annual angioplasties of coronary arteries increased markedly. While 2,524 balloon angioplasties were performed in 1998, the number of procedures increased up to 8,597 by the end of 2005. The number of PCIs performed has continued to grow and now exceeds 12,000 per year. The most significant reason for the increase is the large number of PCI providing centers (21 in 2005) in Finland (Statistics of the Finnish Heart Association: http://www.sydanliitto.fi/en_GB/).

Both PCI and CABG were started in 1994 at VCH. From the year 2000 onwards number of PCI procedures performed exceeded that of bypass operations (Figure 3), which corresponds to the general trends in invasive treatment for CAD.

2.3 Invasive treatment of coronary artery disease

2.3.1 CABG or PTCA/PCI versus medical therapy

Introducing invasive treatment options for CAD initiated trials aimed to study advances of the new treatments compared to traditional medical therapy (MT). Numerous institutional non-randomized studies and randomized prospective studies with a high degree of evidence showed the relative long-term benefit of CABG over medical therapy (MT) on survival and on relief from angina in CAD patients (Appendix 1).

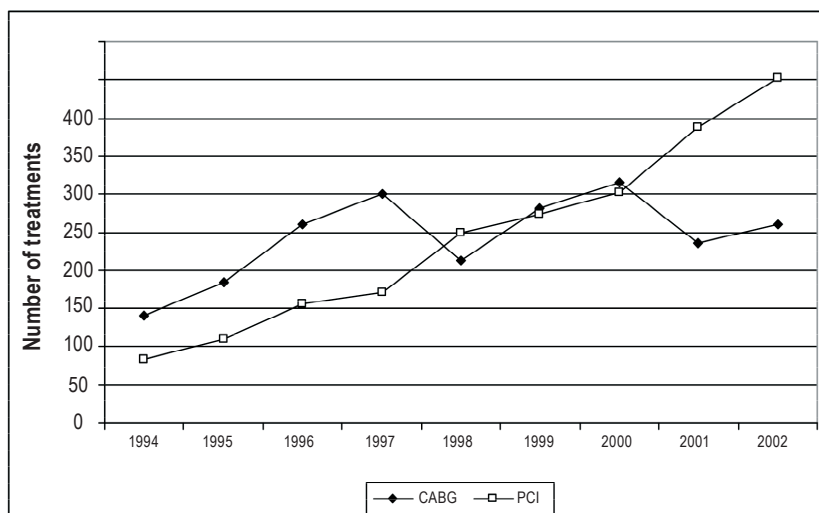


FIGURE 3. Number of invasive treatments performed at VCH until the end of 2002.

2.3.2 CABG versus PTCA/PCI

Outcome after CABG and PCI has been compared in numerous randomized studies. The most significant phenomenon in these studies is the entry bias: the trials included only a minority of patients eligible for both treatment options. A large number of patients were excluded on angiographic grounds, making PCI ineligible as a treatment option. Thus, many trials may not accurately reflect common clinical practice. On the other hand, guidelines, such as those published by ACC/AHA (1991, 2004), are aimed to standardize practice for the invasive treatment of CAD. They are based on a critical review of the literature among retrospective trials, registry studies and prospective randomized studies. Thus, they may attempt to diminish selection bias in comparing treatment options as also confirmed by the European Society of Cardiology (Lenzen et al. 2005). Trials concerning comparisons between CABG and PCI are displayed in Appendix 2.

In general, there is a non-significantly higher in-hospital mortality and significantly higher morbidity after CABG than after PCI. However, total mortality or cardiac related mortality might be equal between these treatments in the follow-up. CABG patients seem to be more frequently free from angina after a long-term follow-up, although patients in both treatment groups perceive improved cardiac-related health status. Moreover, repeat revascularization has been required 5 to 8 times more often after initial PCI than after initial CABG during mid-term or long-term follow-up.

The use of stents started a new technical era among percutaneous interventions. The variations in the conclusions from randomized trials may be explained by the general expectation that stenting will improve previous PTCA results including threatened vessel closure and suboptimal results. Although there were no survival benefits from either of the two revascularization procedures, patients initially treated with CABG needed fewer repeat revascularization procedures and suffered fewer MACE.

The introduction of drug-eluting stents (DES) containing, for example, sirolimus or paclitaxel as effective drugs may reduce the gap in late outcome between PCI and CABG. However, the advance has been controversial when compared to bare metal stents (BMS), and DESs have not provided any advantage in terms of myocardial infarction (MI) or survival according to randomized studies. The most considerable advance may have been a reduction of angiographic restenosis, which may lead secondarily to better clinical outcomes with limited progression of the disease in native vessels (Cutlip et al. 2004, Chieffo et al. 2007). Yock and co-authors concluded in a retrospective cohort study that although frequency of repeat interventions was

high during the first year after PCI, the incremental benefit between the use of BMS vs. DES was smaller than suspected (Yock et al. 2006). According to an editorial review DES have no survival advantage compared with BMS. The review also notes that the current therapy for multivessel disease (MVD) has resulted in relatively high excess mortality in patients with initial stenting as compared with patients with initial CABG in data from real-world registries (Guyton 2006). In general, available data demonstrate lower incidence of MACE and lower need for repeat revascularization after CABG than stenting with DES for MVD.

In addition to the aforementioned studies there is still one, which merits mention. The Synergy between PCI with Taxus and Cardiac Surgery Trial (SYNTAX) was conducted from March 2005 through April 2007 in order to assess the optimal revascularization strategy for patients with MVD or left main stem (LM) stenosis eligible for both treatment options, PCI or CABG. The trial also defined the populations of patients for whom only one revascularization method would be effective. The design of the trial was prospective and clinical and it was performed at a total of 85 locations in 17 countries. The study involved consecutively all eligible patients with three vessel disease (3-VD) or LM stenosis. Patients in whom equivalent revascularization could be achieved with either CABG (897 patients) or PCI with paclitaxel-eluting stent (903 patients) were randomized to undergo one of the two treatment options. The primary objective of the study was to analyze the compound clinical outcome defined as major cardiovascular or cerebrovascular events (MACCE) at 12-month follow-up. The final analysis confirmed that 17.8% of PCI patients and 12.1% of CABG patients presented with MACCE ($p=0.002$). The main reason for the difference was an increased rate of repeat revascularization, 13.5% vs. 5.9% between the groups respectively. The mortality rate was 4.3% vs. 3.5% (NS) and the rate of stroke 0.6% vs. 2.2%, $p=0.003$). The researchers concluded that CABG remains the standard treatment option for patients with 3-VD, since it resulted in lower rates of MACCE at 1 year (Gomes et al. 2008, Serruys et al. 2009).

2.4 HRQoL after CABG

2.4.1 Short-term follow-up

Several studies have reported significant improvement in HRQoL after CABG in short-term follow-up from one month up to 6 months.

Caine et al. accomplished one of the first measurements of changes in patients' perceptions of QoL before and three months after CABG. The study was prospective

and consecutive and included 100 male patients. The differences between NHP scores were significantly improved in all sections of the instrument used, i.e. energy, sleep, physical mobility, social isolation, emotional reaction and pain ($p < 0.01$). Improvement was also evident in the domains general health state, symptoms and activity (Caine et al. 1991).

The study by Chocron and co-workers yielded a congruent result. Pre- and postoperative (after three months) HRQoL was compared in a patient group undergoing CABG. An average of 80% of patients was improved by their operations. Although postoperative scores showed an improvement in all six sections of the NHP for the patient material, age over 70 years and NYHA class 3–4 predicted independently less improvement for the energy section, and NYHA class 3–4 also for physical mobility. Independent predictors for impairment by operation were NYHA class 3–4 in the energy section (OR 3.7, 95% CI 1.4–9.8, $p = 0.01$) and in the physical mobility section (OR 2.4, 95% CI 1.02–5.5, $p = 0.006$), and female gender in the social isolation section (OR 2.8, 95% CI 1.03–7.7, $p = 0.01$) (Chocron et al. 1996). In the study by Ross et al. (2001) the findings were congruent. Subjective perceptions of physical and psychological well being changed significantly and measures of mood state ($p = 0.03$), physical functioning ($p = 0.004$), vitality ($p = 0.007$), and social functioning ($p = 0.002$) improved significantly over time. However, satisfaction with the socio-economic domain decreased significantly from before surgery during the follow-up of three months.

Rumsfeld and co-authors evaluated a total of 1,973 patients enrolled in a multicentre prospective cohort study to find predictors for impaired HRQoL outcome after CABG. Patients completed SF-36 health status surveys preoperatively and after 6-month follow-up. Mean age was 63 years and all patients were male. The mean physical component score (PCS) improved 5.2 points ($p < 0.001$) during the follow-up likewise the mean mental component score (MCS) 1.8 points ($p < 0.001$) indicating overall improvement of HRQoL. The authors found several factors, which predicted both postoperative physical and mental health status, i.e. neurologic or psychiatric disease, peripheral vascular disease, COPD, current smoking, age and preoperative NYHA functional class (Rumsfeld et al. 2004). In Kattainen's study (Kattainen et al. 2005) change in HRQoL was studied in patient data on 615 consecutive CAD patients, of whom 432 underwent CABG. The 15D was used to measure HRQoL. CABG patients experienced a statistically significant improvement in HRQoL by 6 months after the operation. Clinically important improvement was detected in 82% of patients by 6 months, whereas 6% of patients deteriorated correspondingly during the same time period. Subsequent HRQoL did not change significantly between 6 and 12 months and only 26% of patients achieved clinically important improvement

by 12 months (Kattainen et al. 2005). In a study by Elliott and co-authors both the SF-36 and the 15D was used as measures. Scores for physical functioning, role functioning-physical bodily pain, bodily pain, role functioning-emotional and the PCS deteriorated during the hospital stay after CABG ($p < 0.001$), but by contrast, MCS improved slightly from presurgery to hospital discharge measured by the SF-36. Significant improvement was evident on the 15D dimensions mobility, breathing, usual activities, vitality and distress ($p < 0.001$) at the 6-month post-discharge measurement (Elliott et al. 2006).

In a cohort of 183 CABG patients improvement in HRQoL was observed for 6 months after surgery (Le Grande et al. 2006). The SF-36 was used in this study to reflect a patients' overall physical and mental status. The mean age of patients was 65.5 years and 80% were male. PCS improved linearly and significantly by 6 months after the intervention. In the MCS the improvement was rapid during the first two months after operation but leveled out by 6 months. Patients tended to experience a more rapid improvement in emotional status in the early weeks, but return to normal emotional roles and social functioning reduced the trajectory later on. Although HRQoL improved over time, the course of recovery was not linear in all patient sub-groups and the authors emphasized that it is important to identify characteristics of patients together with post-operative symptoms that could be possible targets for intervention to improve HRQoL outcomes.

2.4.2 Mid-term follow-up

Several reports have shown improvement in HRQoL short-term after CABG, followed by stabilization and by a small but significant decline in some scores of physical health and health perception later in the follow-up from 6 months up to 2 years.

In a prospective study of 2,121 consecutive CABG patients HRQoL was assessed three times: before surgery, and at 3 months and 2 years after the operation. Response rate to questionnaires was 82% throughout the study period and total mortality was 7.4% at two years. HRQoL improved on the basis of mean NHP scores significantly within three months ($p < 0.0001$) and 2 years ($p < 0.0001$) after surgery when compared to baseline. Although improvement was seen on all dimensions the major improvement was seen in terms of less pain and increased energy. Similar improvement also concerned the Physical Activity Score and Psychological General Well-being Index for 2 years ($p < 0.0001$ for change in both measures). Although major improvement was seen at 3 months, a slight improvement was detected up

to 2 years postoperatively. Sexual problems were still common 2 years after CABG. Predictive factors were preoperative sexual problems (OR 4.80, 95% CI 3.51–6.57, $p < 0.0001$), male sex (OR 2.94, 95% CI 1.72–5.01, $p < 0.0001$) and diabetes (OR 2.12, 95% CI 1.37–3.30, $p = 0.0008$) (Sjöland et al. 1997).

Hunt et al. found significant improvements in HRQoL measured by the SF-36 in a patient material, which consisted of 123 CABG patients (22 women). Follow-up was 12 months. A significant improvement was seen in physical functioning ($p < 0.001$) bodily pain ($p = 0.024$), social functioning ($p = 0.011$) and role limitations from emotional status ($p = 0.003$). Patients' overall perception of QoL 12 months after surgery was excellent in 19%, very good in 34%, good in 25%, poor in 18% and very poor in 4%. 92% of patients benefited from CABG 12 months ago according to their own perception (Hunt et al. 2000).

In a study by Falcoz et al. 293 open-heart surgery patients were included and followed up for HRQoL for 12 months. The SF-36 was used as an instrument to assess QoL. The study group was mixed, since 50.4% of the patients underwent bypass grafting and 43.6% heart valve replacement (6.0% miscellaneous). HRQoL improved in an average of 50% of patients. Comparison of the scores before and one year after the operation demonstrated a significant improvement in QoL on all but three dimensions (energy, social and general) of the SF-36 scales. The distribution of patients improving (or deteriorating) after surgery did not differ by gender or by type of procedure. The most frequently quoted predictors of impaired HRQoL were NYHA functional class 3 or 4 and angina class 3 or 4 (Falcoz et al. 2003).

In a large prospective study by Järvinen et al. a total of 508 isolated CABG patients were assessed for changes in HRQoL for 12 months after surgery using the RAND-36 as a measure. Overall performance status (Karnofsky score) (Karnofsky and Buchenal 1949) and symptom status (NYHA class) were also included. The mean age of the cohort was 62.3 years (SD 9.3) and 82.7% were male. 12-month survival was 96.7%. The researcher found that scores characterizing HRQoL improved significantly compared to baseline level in patients with different age, sex, left ventricular function and diabetes status. The only exception was the MCS, in which the improvement did not reach a statistically significant level among patients over 75 years. Also, the overall benefit from CABG was less among elderly patients than in patients of age under 75 years (Järvinen et al. 2003). In Kattainen's study HRQoL did not subsequently change between 6 and 12 months despite of significant improvement until 6 months after treatment. Only 26% of patients achieved clinically significant improvement by 12 months (Kattainen et al. 2005).

2.4.3 Long-term follow-up

Long-term (over 2 years after surgery) change in HRQoL of CABG patients has been discussed in only few earlier reports. Development of HRQoL is characterized by deterioration during a longer follow-up after the operation.

Caine et al. followed up 100 CABG patients throughout 5 years. In comparing the five-year results to those at one year, slight improvements were seen in NHP dimensions of pain, sleep, social isolation and emotional reactions. Deterioration was noted in the physical mobility and energy scores. Absence of dyspnoea before surgery (relatively good left ventricular function) was a predictor of good outcome at both one and five years. The role of vein graft patency was discussed as a contributory factor to the finding (Caine et al. 1999).

Herlitz and co-authors have also published studies on long-term development and changes in HRQoL. After five years of follow-up impairment was seen in HRQoL as compared to the time before surgery. Independent predictors of an impaired QoL were female sex (OR 2.1, 95% CI 1.6–2.9, $p < 0.00001$), diabetes (OR 2.1, 95% CI 1.4–3.0), claudication (OR 2.5, 95% CI 1.7–3.8, $p < 0.00001$), chronic obstructive pulmonary disease (COPD) (OR 2.8, 95% CI 1.4–5.5), obesity (OR 1.8, 95% CI 1.2–2.5) and previous CABG (OR 2.3, 95% CI 1.3–3.9) (Herlitz et al. 1999). Later on, 10 years after the startup of the study 68% of patients were still alive. Independent predictors of an inferior HRQoL with all three measures used were a history of diabetes (OR 1.9, 95% CI 1.1–3.2, $p = 0.05$) and COPD (OR 6.1, 95% CI 1.4–27.2, $p = 0.02$). Moreover, high age at the time of operation, female gender and history of hypertension predicted impairment in HRQoL with two of the instruments used (Herlitz et al. 2003). In the same material 54% of survivors were free from chest pain and 31% free from dyspnoea 10 years after surgery (Herlitz et al. 2005, Herlitz et al. 2008). Lukkarinen and co-workers' study measured HRQoL and its changes in 8-year follow-up among CABG, PTCA and MT patients using the NHP. CABG patients had better HRQoL 8 years after the operation than at baseline on the dimensions of mobility ($p < 0.001$), energy ($p = 0.003$), and pain ($p = 0.031$). PTCA patients had better HRQoL 8 years after the intervention on the dimensions of emotional reactions ($p = 0.002$), pain ($p = 0.003$), mobility ($p = 0.004$), and energy ($p = 0.005$). Patients with MT experienced no significant change in HRQoL during follow-up. The authors concluded that both CABG and PTCA improve CAD patients' HRQoL still 8 years after the intervention (Lukkarinen et al. 2006).

2.4.4 HRQoL by gender after CABG

Studies concerning outcome have shown that female patients may have poorer outcome after CABG surgery. Although studies have not been entirely consistent, the long-term results in terms of symptom status, functioning and HRQoL tend to be less satisfactory in women than in men. Women may experience less relief from angina and they may suffer more from dyspnoea and have lower functional status than men. Actually, the literature has yielded conflicting results on gender differences in physical and emotional outcomes after CABG. In contrast to these reviews some other studies have shown no significant gender-related differences in symptoms and functional outcomes during the first year after the bypass surgery.

Abramov et al. (2000) conducted a registry-based study in which the role of female gender was assessed as an independent risk factor for outcome. Data on 4,823 patients (19.3% female) was analyzed after a follow-up of 9 years. Early mortality rate was 2.7% in women versus 1.8% in men ($p=0.088$), frequency of perioperative MI 4.5 vs. 3.1 ($p=0.043$), and rate of cerebral accidents 2.4% vs. 1.8% ($p=0.23$). The rate of MACE was 8.4% in women and 5.9% in men ($p=0.007$). Recurrent angina class 3 or 4 was more frequent in women than in men at 5 years (15.2% vs. 8.5%, $p=0.001$). 5-year survival rate was 93.1% in women and 90.0% in men. After adjustment for other risk variables, female gender was protective for long survival (RR 0.40, 95% CI 0.16–0.74, $p<0.005$). Contrary to that, Guru et al. reported similar survival between male and female CABG patients despite more complex preoperative status of women (Guru et al. 2006).

Using the SF-36 health survey Vaccarino and co-workers studied physical and physiological functional gains in a consecutive cohort of 777 male and 295 female CABG patients. Females were older than males (69.6 years vs. 64.2 years, $p<0.0001$), had unstable angina more often (36.3% vs. 26.8%, $p=0.003$), likewise congestive heart failure (14.2% vs. 7.1%, $p=0.0003$), more severe class of angina (CCS 3–4) ($p<0.0001$) and lower PCS and MCS of the SF-36 ($p<0.001$ and 0.0003 respectively). Males fared worse in number of diseased vessels and in number of grafted vessels ($p=0.0002$ and $p<0.0001$ respectively). 2.6% of men and 2.2% of women died within 6 months after surgery (NS). At 6 months both men and women showed a significant improvement in both physical functioning and in mental health. However, men improved more than women and their PCS change was over 3 times greater than in women ($p<0.0001$). The proportion of patients whose score improved was twice as great in men as in women (64.2% vs. 34.0%, $p<0.001$). Conversely, the proportion of patients who deteriorated was twice as great in women as in male ($p<0.0001$). Analysis of mental health scores showed similar rates. Mean mental score change was

-2.9 in favour of men ($p=0.004$). Female patients moreover had 53% higher hospital readmission rates than men during the follow-up. The authors' explanations for these findings were possible less complete revascularization and higher graft occlusion rates attributed to women's smaller coronary arteries. Another explanation lies in a potential sex difference in referral for diagnosis and treatment for CAD. Females may have more severe CAD at the time of diagnosis and surgery. Gender differences in self-reporting of health status may also play a role: women consistently report worse health than men, possibly because of cultural and social aspects associated with gender (Vaccarino et al. 2003).

Phillips-Bute and co-workers arrived at a parallel conclusion. Although QoL improved in both genders female patients experienced poorer outcome in terms of subjective cognitive difficulties, increased anxiety, diminished work related activities (SF-36) and reduced exercise capacity as assessed by the Duke Activity Status Index (DASI) (Hlatky et al. 1989). A possible explanation for the diminished QoL benefit from surgery may be that women's compromised QoL is less related to cardiac health than is men's QoL and therefore less responsive to cardiac intervention. The causes of lower preoperative QoL may be more environmental and/or personality-related for women than for men. This could account for the observed differences in improvement (Phillips Bute et al. 2003). However, Jokinen et al. did not find difference in perceived HRQoL between male and female CABG patients during a follow-up, the mean of which was 9.6 years (Jokinen et al. 2001).

Lindquist and co-workers (2003) concluded that although physical, social and emotional functioning, as well as recovery after CABG was similar between men and women, HRQoL scores remained less favourable to females. Basically there were more females over 65 years age (45.2% vs. 59.5%, $p<0.01$). After 6 weeks both men and women had less anxiety and depression than before surgery ($p<0.01$) and by six months after surgery both genders improved in social and physical functioning ($p<0.01$) but female patients scored lower HRQoL than men throughout the follow-up of twelve months. Koch et al. aimed at determining the HRQoL of patients undergoing CABG in a sample of 1,825 patients, of whom 483 were women and 1,342 were men. The finding for gender difference in HRQoL was that both baseline and follow-up scores of functionality were significantly lower for women than for men. Also, after adjusting for preoperative demographics and co-morbid conditions, operative factors and postoperative morbidities, women continued to achieve significantly lower functional status after CABG than men (Koch et al. 2004).

In a study by Falcoz et al. both genders showed a significant improvement in all QoL scores. This positive change followed two-slopes-shaped line both in men and in women. Thus, after a sharp increase between the preoperative period and 1

year, there was stabilization until 2 years. Two-year follow-up showed a significant and similar improvement in both genders in terms of HRQoL, although women had lower baseline scores. The best independent predictive factor of two-year cardiac functional status was the baseline PCS in women and the baseline MCS in men (Falcoz et al. 2006). Female patients in Gjejlo's study (Gjejlo et al. 2006) also reported significantly lower scores than male patients on three subscales of the SF-36 (physical function ($p < 0.001$), role physical ($p = 0.001$) and vitality ($p = 0.003$) after 3 years of follow-up. In another study by Gjejlo, HRQoL demonstrated a clear overall improvement over the first year after the CABG for both genders. Repeated measures analysis of variance showed that the improvement was two-sloped: after a distinct increase between baseline and 6 months, scores stabilized between 6 and 12 months. On single dimensions of the SF-36 female patients scored significantly lower than male patients. The difference diminished when all three measurements (preoperative, six months and twelve months) were tested: gender difference was seen only in role emotional ($p = 0.025$) and in bodily pain ($p = 0.046$) (Gjeilo et al. 2008).

In an analysis of a large patient sample (total $n = 2,121$, women 401) Sjöland et al. reported that HRQoL was poorer in women than in men at each follow-up period (3 months, 12 months and 24 months) but they observed no gender-related differences in change of measured dimensions of HRQoL (Sjöland et al. 1999). Järvinen and co-authors in their study also noted that men and women benefited equally well from CABG. The researchers examined 508 CABG patients 12 months after surgery and observed a significant improvement on all eight dimensions of the RAND-36 in the majority of patients and in both genders. Patients aged over 75 years derived less benefit in terms of certain aspects of HRQoL, especially the mental component, regardless of gender (Järvinen et al. 2003). Falcoz et al. (2006) found that the improvement was equal in both genders two years after cardiac surgery and in a small patient sample examined by Baldassarre and co-authors HRQoL improved significantly in women over 61 years of age, but the observation time was short, only 3 months (Baldassarre et al. 2002).

2.4.5 HRQoL by age after CABG

Cardiac surgery has been performed with increasing frequency on patients in older age, even octogenarians. HRQoL outcome is especially important in older ages, as the overall operative risk is high. Cardiac surgery in the elderly can be performed with acceptable morbidity and mortality and with a dramatic improvement in

functional status i.e. in patients >70 years (Chocron et al. 2000, Engoren et al. 2002), in patients >75 years (Mittermair et al. 2002) and in patients over 80 years (Fruitman et al. 1999, Zingone et al. 2009). Despite increasing use of CABG in the elderly, little data is available on elderly patients' health status benefits from CABG. Age has been mentioned in several studies as a predictor of impaired HRQoL after CABG. However, the reports of HRQoL outcome are controversial.

The first QoL assessments of CABG patients in older ages were performed using the Karnofsky score. Studies by Glower et al. (1992) and by Kumar and co-authors (1995) demonstrated that CABG could be offered to selected elderly patients with marked improvement in performance status and with improved QoL. Later on Fruitman et al. studied a patient group older than 80 years at the time of CABG surgery (mean age 83 years). Follow-up was mean 15.7 months. The material included not only CABG patients (65.4%) but also CABG with valve replacement or isolated valve replacements (30.2%). By the end of follow-up the study group achieved at least an equal level of HRQoL as compared to general population of >65 years. Thus, physical functioning and energy were equal ($p=0.73$ and $p=0.49$, respectively). Patients were significantly better in role limitations of physical health ($p=0.0003$) or of emotional health ($p=0.00001$). Emotional wellbeing ($p=0.0001$) and social functioning ($p=0.01$) were also at a higher level than in general population (Fruitman et al. 1999). Chocron and co-authors evaluated improvement and predictors of improvement in older patients' HRQoL after cardiac surgery. The data consisted of 377 patients from three centres with a mean age of 74 ± 3 years, 10% were over 80 years old. HRQoL was assessed by the NHP and followed up for two years. Postoperative scores improved in all but the social isolation domain and remained similar at one and two years after the intervention. In logistic regression analysis predictors of impaired HRQoL outcome were age >75 years (OR 1.8, 95% CI 1.02–3.2), CAD (OR 2.4, 95% CI 1.04–3.6), postoperative adverse events (OR 1.9, 95% CI 1.01–3.7), diabetes (OR 2.4, 95% CI 1.2–4.7) and physical mobility impairment (OR 3.4, 95% CI 1.3–8.7). The conclusion was that cardiac surgery improved self-perceived health status in patients over 70 years, but the improvement was greater in aortic valve surgery patients (Chocron et al. 2000). According to Pierson and co-authors older patients may attain good self-reported functional outcomes after surgery; however, the time course for recovery is more protracted than for younger patients (Pierson et al. 2003). In Rumsfeld's analysis (Rumsfeld et al. 2004) age per 10-year increment predicted improved mental health status at six months after CABG (parameter estimate 0.83, SE 0.30, $p=0.005$).

In Järvinen's study (Järvinen et al. 2003) 10% of CABG patients were over 75 years old. The mean of RAND-36 PCS scores improved significantly among elderly

patients during 1-year follow-up ($p < 0.001$). However the mean changes in MCS scores did not reach a statistically significant level in this age group ($p = 0.097$). Repeated measures analysis of variance revealed a significant age by change interaction for PCS, indicating a less steep improvement for the oldest subgroup of patients. Compared to younger patients, patients >75 years improved less markedly in PCS scoring ($p = 0.042$) and MCS scoring ($p = 0.048$). Thus, elderly patients derived less benefit in terms of certain aspects of HRQoL. The authors emphasized that it might be important in clinical practice to consider the age-related aspects of outcome, rather than QoL.

Conaway and co-authors studied symptoms, function, and quality of life changes in elderly patients undergoing CABG in a follow-up of one year. In-hospital mortality was similar (2.6% vs. 2.2%, NS), but one-year mortality was greater in older patients (11.5% vs. 5.4%, $p = 0.008$). Among survivors, similar health status benefits were observed one year after surgery as measured by the Seattle Angina Questionnaire (SAQ). SAQ score change was for physical function 21.5 ± 27.0 vs. 19.7 ± 27.0 , $p = 0.67$; for angina frequency 30.1 ± 25.7 vs. 24.6 ± 25.6 , $p = 0.07$; and for QoL 37.7 ± 21.8 vs. 33.6 ± 25.2 , $p = 0.16$). The age-time interaction term was significant ($p = 0.003$), confirming a slower recovery of physical function, but angina relief and QoL improvement did not differ by age. Despite a slower rate of physical recovery, older patients derived similar health status benefits from CABG compared with younger patients. The authors commented that age alone should not be a deterrent for recommending bypass surgery (Conaway et al. 2003). Recommendation for active treatment in advanced ages was concluded also in the study performed by Huber et al. A remarkable QoL and important improvement in the functional status after cardiac surgery was seen in patients over 80 years. Also satisfactory medium-term survival justified early intervention for heart disease in this age group (Huber et al. 2007). In Markou and co-workers' study 568 patients undergoing a primary isolated CABG for stable angina were followed up 12 months postoperatively. The variables evaluated were HRQoL measured by EuroQoL, physical activity status and symptomatic status according to NYHA classification. Analysis was based on three age groups, age <65 years, $65-74$ years and >75 years. The study concluded that elderly patients achieved the same improvement in their symptomatic status as younger patients. However, they benefited less from CABG regarding to their QoL and physical activity (Markou et al. 2008). In a recent article by Jokinen et al. the key finding was that patients who underwent CABG in older age (>70 years at the time of operation) achieved HRQoL and survival comparable with that of the age and gender matched reference population (Jokinen et al. 2008).

2.4.6 HRQoL after PTCA/PCI

HRQoL assessments after PTCA/PCI have been usually performed in connection with assessments of HRQoL for CABG patients. The literature contains only a few reports with HRQoL assessment exclusively after PTCA or PCI.

The first randomized study in which perceived health status was assessed also after PTCA was the RITA trial. Both CABG and PTCA patients showed a marked improvement compared with the baseline in all domains of the NHP. Patients in the CABG group were slightly better than those in the PTCA group in all six dimensions of the NHP at 6 months. When all 38 items in Part 1 of the NHP were combined, the mean reductions in the number of items affected were 4.83 in the PTCA group and 6.04 in the CABG group compared with baseline at 6 months. The mean difference in favour of CABG was thus 1.21 items (95% CI 0.33–2.09, $p=0.007$). This difference was reduced to 0.79 ($p=0.10$) at 2 years of follow-up. Patients' perceptions whether their health was causing problems in various aspects of living according to NHP revealed that there was marked improvement in both PTCA and CABG patients until 2 years compared with baseline. The prevalence of health-related problems was slightly but insignificantly greater in the PTCA group than in the CABG group. The proportion of patients with impaired HRQoL diminished by more than half by 6 months. At baseline the patients' grade of angina had a marked relationship with all domains of perceived health status. During the follow-up there was a clear trend whereby the higher the angina grade, the greater the impairment. Patients with residual angina after 2 years seemed to have impaired HRQoL, too. Thus both interventions produced similar benefits in HRQoL over several years and possible difference in HRQoL was related to angina status (Pocock et al. 1996).

The BARI study evaluated functional status using the DASI and emotional health using the RAND-36 in a comparison of PTCA and CABG patients. Improvement in functional status as assessed by the DASI was significantly greater among CABG patients than that of PTCA patients up to three years. After four and five years the difference diminished and was no longer significant. Emotional health also improved significantly with no significant difference between the groups. CABG was associated with a better QoL than PTCA for three years, after the initial morbidity caused by the procedure (Hlatky et al. 1997). In the CABRI study an optional QoL substudy was also set up. Perceived health status was assessed at baseline and 1 year after revascularization by means of the NHP. 154 main study patients (15.4%) participated. Total score, and thereby HRQoL, improved significantly in both groups with score change mean -11.9 ($p<0.001$) for the CABG group and -8.7 ($p<0.001$) for the PCI group. General well-being improved in both groups ($p<0.001$ for CABG and

$p=0.004$ for PTCA). There was no correlation between change in the NHP score and angina class when adjusted for baseline values ($p=0.20$), but CABG patients achieved an apparent more favorable outcome in degree of perceived energy. No difference between males and females was detected (Währborg 1999). Brorsson and co-researchers followed up a consecutive series of patients with 1-VD or 2-VD who underwent CABG ($n=252$) or PTCA ($n=349$). Outcome measures were survival, angina frequency and HRQoL as assessed by the Swedish Quality of Life Survey (SWED-QUAL) (Brorsson et al. 1993). Both bypass surgery and angioplasty led to improved quality of life. Bypass patients achieved better state of QoL at six months but by 48 months QoL was similar for patients initially treated by either procedure (Brorsson et al. 2001).

A study by Borkon et al. compared health status after PCI and CABG using the SAQ. The patient material was not randomized. PCI patients required repeat PCI or CABG more frequently within 6 months (19% vs. 0.5%, $p<0.01$). CABG patients had a greater degree of angina relief over 12 months ($p<0.005$) and multivariate analysis confirmed that CABG was an independent predictor for it ($p<0.001$). CABG patients experienced a significant impairment in physical function during the first month after the intervention but the function recovered from the second postoperative month on to the level of PCI patients. Both PCI and CABG patients experienced a time-dependent improvement in risk-adjusted QoL. However, CABG patients achieved higher QoL scores at 6 months and at 12 months ($p<0.004$). The authors' conclusion was that the adverse influence of restenosis negatively influenced HRQoL outcome for PCI patients (Borkon et al. 2002). Rumsfeld and co-workers randomized CAD patients with medically refractory ischemia to PCI and CABG and found equal six-month HRQoL between the groups. The authors concluded that HRQoL could not be a criterion for selection of a revascularization procedure for these patients (Rumsfeld et al. 2003).

In Kattainen's study (Kattainen et al. 2005) HRQoL was studied in patients undergoing either CABG or PTCA and using the 15D as measure. Patients in both treatment groups were on average significantly poorer in their baseline QoL when compared to general population matched by age and gender ($p<0.001$). After the intervention HRQoL scores improved statistically in both groups by 6 months but did not reach the average score level of the population. Moreover, no significant change took place during the second half of the follow-up until 12 months. When the two groups were observed separately, no more significant change was detected, although 26–36% of patients experienced either a clinically important improvement or deterioration. The results suggested that PTCA patients did not achieve clinical improvement in HRQoL similar to that of CABG patients (Kattainen et al. 2005).

Moreover, the sense of coherence was more stable among CABG patients than PTCA patients. In the PTCA group the sense of coherence actually decreased during follow-up (Kattainen et al. 2006). Another Finnish study by Lukkarinen and co-writers measured HRQoL changes during 8-year follow-up between CABG, PTCA and MT patients. CABG patients had significantly better HRQoL 8 years after the operation than at baseline on the dimensions of mobility ($p < 0.001$), energy ($p = 0.003$), and pain ($p = 0.031$). PTCA patients had statistically significantly better HRQoL at the same time on the dimensions of emotional reactions ($p = 0.002$), pain ($p = 0.003$), mobility ($p = 0.004$), and energy ($p = 0.005$). Patients on medication experienced no significant change in HRQoL during follow-up. Both CABG and PTCA improved HRQoL of CAD patients still 8 years after the intervention (Lukkarinen et al. 2006). The MASS-II study also compared HRQoL of patients undergoing CABG, PCI and MT as therapeutic strategies for stable CAD in a 1-year follow-up of. There was a greater proportion of angina-free patients in the CABG than among PCI or MT patients ($p < 0.001$). Moreover, 10.8% of MT patients and 13.3% of PCI patients underwent more additional interventions than CABG patients with only 0.5% ($p < 0.001$). All three interventions showed improvement over the first year in most aspects of QoL measured by the SF-36, especially in physical role functioning, general health, vitality and pain. Both PCI and CABG patients showed significant improvement at 6 months as well as at 12 months and both groups sustained a better level of HRQoL in comparison to MT patients. CABG patients showed greater and more progressive improvement of QoL (Favarato et al. 2007).

QoL analyses were also performed in the SYNTAX study (Serruys et al. 2009), where the study participants completed self-administered questionnaires probing CAD-specific quality of life, including angina frequency and physical limitations together with general physical and mental health using the SF-36 as the instrument. The results have been presented so far as a short report in a clinical-trial session of American College of Cardiology 2009 Scientific Sessions. For QoL measures, such as physical limitations and treatment satisfaction, patients treated with DES tended to report feeling significantly better than CABG patients within the first few months, but these differences disappeared by six or 12 months. The path to one-year QoL outcome is different in CABG-treated vs. DES-treated patients. Thus the bypass patients have an extended period of disability in the first month and then make a recovery. The PCI patients recover more quickly, which means that when integrating QoL with duration PCI may have yield a benefit of at least for one year (Cohen D, i2 Summit at the American College of Cardiology 2009 Scientific Sessions, unpublished data) (<http://www.theheart.org>).

2.4.6.1 HRQoL after medical therapy

Some studies on HRQoL after PCI versus MT can be found in the literature. Also these have yielded contradictory results.

The RITA-2 trial study evaluated HRQoL between PTCA patients and MT patients through the SF-36 until 3 years after randomization. The conclusion was that PTCA substantially improved the perception of QoL when compared to MT. The PTCA group achieved significantly greater improvements in physical functioning, vitality and general health at three months and at 1 year after randomization. However, no difference was seen between the groups by 36 months. The superiority of the PTCA group over the MT group was related to breathlessness, angina grade and treadmill exercise time at baseline and after one year. Moreover 27% of MT patients underwent interventions in the interim. Alleviation of cardiac symptoms was attributed to differences between the study groups, but it must be balanced against the small procedure-related risks of PTCA (Pocock et al. 2000). The COURAGE Study confirmed the conclusions of a former randomized study (RITA-2) between PTCA treated patients and patients with MT alone. Besides of angina-specific health status HRQoL was assessed with the use of the RAND 36-item health survey. HRQoL improved in both groups at 1 and 3 months but with an advantage for PCI over MT at 3 months for five domains. Although at 6 months an advance for PCI over MT was seen and the PCI group was more likely to have a clinically significant improvement when compared to baseline status, no advantage was observed one year after randomization. PCI plus optimal MT relieved angina and improved HRQoL to a greater extent than MT alone. The more severe the angina was before PCI, the greater was the benefit to those patients (Weintraub et al. 2008).

2.4.7 Predictors of HRQoL after CABG

Several studies have reported predictors of HRQoL after CABG. Both biological and medical characteristics have been associated with poorer HRQoL outcomes. Of course, the same variables may impair general outcome also and have an impact on morbidity and even on survival. The most common preoperative variables, which may have impact on postoperative HRQoL, are listed in Table 1.

TABLE 1. Predictors for HRQoL after CABG

Variable	Comment	Reference
Preoperative cardiac function	1,934 patients were evaluated prospectively for 6 months. 34% of patients were initially in NYHA class 3 or 4. High NYHA class predicted impaired mental health status (parameter estimate -0.91, SE 0.54, $p=0.002$) but had less impact on physical health status.	Rumsfeld et al. 2004
Severity of angina	75.2% of patients were in CCS class 2-4 before CABG. At six months 67.7% of patients were free from angina. High CCS (3-4) correlated with poorer baseline HRQoL than low CCS ($p<0.001$ for all domains). After 6 months HRQoL improved significantly in all CSS classes. Serious chest pain predicted independently HRQoL improvement.	Peric et al. 2006
Low left ventricular ejection fraction	EF<50% predicted impaired physical health status after CABG in follow-up of 6 months (RR -1.24, SE 0.44, $p=0.005$).	Rumsfeld et al. 2004
	Low preoperative EF predicted impaired physical mobility at 6 months after CABG (OR 0.73, 95% CI 0.56-0.95, $p=0.047$).	Peric et al. 2006
Diabetes	Non-diabetics scored significantly higher in all domains of HRQoL both preoperatively and at 24 months after CABG.	Yun et al. 1999
	Diabetic patients had poorer HRQoL than non-diabetics 1 year after CABG. The difference was significant both in physical ($p=0.003$) and in emotional ($p=0.0004$) role limitation.	Lindsay et al. 2000
	OR for impaired HRQoL was 2.1 (95% CI 1.4-3.0, $p=0.0002$) among diabetics 5 years after CABG. After 10 years the same tendency was still seen and OR for impairment was 1.9 (95% CI 1.1-3.2, $p=0.01$)	Herlitz et al. 1999 Herlitz et al. 2003
	14.6% of CABG patients were diabetics. Although preoperative HRQoL was poorer, diabetics achieved an improvement in PCS and MCS scores ($p<0.001$). Diabetes was not an independent predictor of impaired HRQoL.	Järvinen et al. 2005
	Diabetes was independent predictor for impaired PCS (β -coefficient -2.49, 95% CI -3.74- -1.24, $p<0.001$) and for MCS (-1.43, 95% CI -2.80- -0.06, $p=0.04$) in long-term survivors (20 years).	Bradshaw et al. 2006
	Diabetes impaired physical mobility section of NHP 6 months after CABG (OR 8.09, 95% CI 2.04-32.09)	Peric et al. 2008
COPD	COPD patients had poorer perceived HRQoL especially with physical limitation 24 months after CABG than patients with normal preoperative respiratory function.	Yun et al. 1999
	COPD on medication predicted inferior HRQoL 5 years after CABG (OR 3.2, 95% CI 1.2-8.7, $p=0.03$)	Herlitz et al. 1999
	COPD predicted poorer physical health status 6 months after CABG (RR -1.75, SE 0.72, $p=0.015$)	Rumsfeld et al. 2004

Cerebral vascular disease	Cerebral vascular disease impaired five-year HRQoL outcome in CABG patients (OR 2.0, 95% CI 1.1–3.6, $p=0.02$).	Herlitz et al. 1999
	Chronic cerebral vascular disease was independent predictor for impaired physical domains of HRQoL in a follow-up of 6 months after CABG (RR -3.17, SE 1.35, $p<0.019$).	Rumsfeld et al. 2004
Peripheral vascular disease	Claudication, reflecting peripheral atherosclerosis predicts independently poorer HRQoL after CABG at five years of follow-up (OR 2.2, 95% CI 1.2–8.7, $p=0.004$)	Herlitz et al. 1999
	Peripheral vascular disease impaired severely physical domains of outcome of CABG patients 6 months postoperatively (RR -2.28, SE 0.51, $p<0.001$)	Rumsfeld et al. 2004
Obesity	Obesity worsens perceived HRQoL of CABG patients in a long-term follow-up of 10 years.	Herlitz et al. 2005
	19.7% of CABG patients were obese (BMI >30 kg/m ²). Morbidity was more frequent, i.e. superficial wound infection (19.0% vs. 7.1%, $p<0.001$), impaired renal function (31.7% vs. 14.4%, $p=0.01$) and mediastinitis (2.0% vs. 1.2% $p=0.55$). HRQoL was poorer compared to non-obese patients at baseline. The improvement in PCS and MSC summary scores was highly significant ($p=0.001$) for obese patients. Obesity was not an independent predictor for adverse HRQoL outcome.	Järvinen et al. 2007
Smoking	Cigarette smoking predicted independently both impaired physical role ($p=0.05$) and emotional role ($p=0.008$) domains of SF-36 after CABG.	Lindsay et al. 2000
	Smoking impaired physical (RR -1.16, SE 0.52, $p=0.027$) and mental (RR -1.63, SE 0.63, $p=0.010$) health status 6 months after CABG.	Rumsfeld et al. 2004

One of the largest analyses on predictors of postoperative HRQoL is that by Rumsfeld et al. (2004). The authors evaluated in total of 1,973 patients and used the SF-36 health status surveys and multiple linear regressions to identify the significant independent predictors of quality of life. Analysis revealed several variables as predictors of impaired physical health status by 6 months: chronic neurologic disease (Parameter Estimate -3.17, $p=0.019$), peripheral vascular disease (-2.28, $p<0.001$), COPD (-1.76, $p=0.015$), hypertension (-1.33, $p=0.003$), current smoking (-1.16, $p=0.027$), lower forced expiratory volume (-1.19, $p<0.001$), lower left ventricular EF (-1.24, $p=0.005$) and lower preoperative MCS score (-0.85, $p<0.001$). Similarly independent predictors of lower MCS scores at 6 months were psychiatric disease (-5.77, $p<0.001$), COPD (-2.4, $p=0.012$), current smoking (-1.63, $p=0.010$), NYHA Class 3 or 4 (-0.91, $p=0.002$) and low preoperative PCS score (-0.91, $p=0.002$) (Rumsfeld et al. 2004).

2.4.8 Impact of obesity

Obesity appearances still more often in the material of CAD patients referred to invasive treatments. Although obesity did not increase postoperative complications related to CABG apart from sternal wound infection (Birkmeyer et al. 1998), obesity in diabetic patients was associated with significant morbidity, i.e. increased risk of postoperative respiratory failure, ventricular tachycardia, AF, renal insufficiency and leg wound infection (Pan et al. 2006). In Järvinen's study obese patients had more morbidity in comparison to non-obese patients, i.e. superficial wound infection 19.0% vs. 7.1%, $p < 0.001$ and impaired renal function (31.7% vs. 14.4%, $p = 0.01$) (Järvinen et al. 2007). In the series of the BARI patients no difference was observed in the in-hospital adverse events according to BMI but the adjusted relative risk of five-year cardiac mortality grew linearly according to BMI (linear $p < 0.001$) (Gurm et al. 2002) and in a study performed by Gruberg et al. over-weighted or obese patients had significantly better outcome than those with normal BMI with regard to survival without MACE (Gruberg et al. 2005). Impact of obesity on HRQoL is still controversial, as seen in Table 1, but difference in HRQoL outcome between obese and non-obese patients may be unsubstantial.

2.4.9 Psychological variables and HRQoL outcome

Symptoms of depression or anxiety have been associated with a marked alteration in mental HRQoL and poorer outcomes after CABG. Preoperative depression and anxiety often predict the occurrence of similar symptoms or psychopathology after surgery (Duits et al. 1997). Mallik et al. conducted a prospective study among CABG patients to investigate the role of preoperative depressive symptoms on postoperative HRQoL. Depressive symptoms were evaluated using the Geriatric Depression Scale (GDS) and physical function using the PCS score of the SF-36. Patients with high preoperative GDS scores (high risk of depressive symptoms) were younger, less educated, had less social support, were unmarried, living alone and were more likely to have been prescribed medication for depression. At 6 months a strong association was found between higher level of depressive symptoms at baseline and improvement in physical function. The rate of physical function improvement was 60.1% in low grade of preoperative GDS scores, 49.8% in moderate grade of GDS scores and 39.7% in high grade of GDS scores ($p = 0.002$ for trend). In multivariate analysis, high grade GDS scores (RR 0.62, 95% CI 0.19–0.82) tended to be a stronger inverse risk factor for functional improvement than traditional measures of disease severity such as

previous MI (RR 0.86, 95% CI 0.70–1.02), heart failure on admission (RR 0.70, 95% CI 0.45–0.96), diabetes (RR 0.78, 95% CI 0.63–0.93) and left ventricular EF, which was not associated with functional improvement (RR for EF >40% compared with EF <40%: 1.09, 95% CI 0.95–1.25) (Mallik et al. 2005).

2.4.10 Preoperative health status and HRQoL

Rumsfeld and co-authors studied the relationship between preoperative health status and changes in QoL following CABG. Improvement in QoL was seen if preoperative health status was inferior. The study revealed that CABG patients had depressed preoperative health status with a lowered MCS and low PCS in comparison to the age-group-matched general population. Mental health status improved modestly for the total study population. Patients with the lowest MCS experienced the greatest mean improvement in mental health status, meanwhile patients with high preoperative MCS score deteriorated. Changes in physical health status were analogous to those seen for mental health status: mean PCS scores improved following CABG surgery for the study population and the patients with lowest preoperative scores experienced the greatest improvement in physical health status following surgery. On average, patients with high physical performance capacity did not experience improvement in physical health status. Preoperative health status was the major and independent determinant of change in QoL following surgery. Patients with relatively low preoperative scores were likely to improve their quality of life, in contrast to the patients with high scores. Angina or other clinical characteristics did not correlate similarly with postoperative QoL (Rumsfeld et al. 2001). Noyez et al. made a parallel finding. They found that CABG patients with relatively poor preoperative HRQoL estimated by the EuroQoL had better postoperative QoL one year after treatment. Conversely, patients with a good preoperative HRQoL might lose a lot of it (Noyez et al. 2006). In a study by Ho et al. low HRQoL may predict higher mortality in older ages (>65 years) after cardiac surgery but not in younger patients (Ho et al. 2005).

2.4.11 Operative complications and HRQoL

Complications during the operation may also impact upon HRQoL, but these variables have not been extensively examined (Rumsfeld et al. 2004). Besides neurocognitive complications impact of perioperative myocardial infarction (PMI) on postoperative HRQoL has also been reported.

In the study by Järvinen et al. (2004) incidence of perioperative MI was 16% among patients undergoing elective CABG. Compared to patients without PMI patients with PMI were older ($p=0.001$), had higher risk according to EuroSCORE ($p<0.001$), suffered more often from rest angina in the week of preceding the operation ($p=0.034$) and more often had a history of stroke ($p=0.018$). PMI patients had sequential anastomoses more often ($p=0.029$). Mean aortic cross-clamp time and CPB time was longer in the PMI group ($p<0.001$ for both variables). 30-day mortality rate was 6.3% in the PMI group and 1.0% in the non-PMI group ($p=0.001$). However, PMI patients achieved better HRQoL ($p<0.001$) by 12 months after the operation and the progress was similar to that of non-PMI patients. As 38% of PMI patients actually showed a small negative change in their general health scores, a multivariate logistic regression analysis was performed for suspected predictors of poorer general health scores. In this analysis PMI was seen to have an independent predictive value with OR 1.78 (95% CI 1.04–3.07, $p<0.05$).

Improvement of HRQoL has also been reported even for survivors with critical complications after CABG. Dimopoulou and co-authors evaluated a CABG patient cohort of 29 patients who experienced cardiac arrest during the first 24 hours after surgery. 79% of patients survived to hospital discharge and 55% of them survived long-term and were alive after four years. None of them had neurologic deficit and their functional status was good, 75% being in NYHA class 1. HRQoL was assessed with the NHP. Data revealed a good level of HRQoL including active social life, sexual activity, special interests and hobbies (Dimopoulou et al. 2001).

In a study by Isgro et al. long-term need for treatment in the ICU after cardiac surgery was burdened by a high in-hospital and early follow-up mortality. Physical and psychological recovery was still excellent during a follow-up of 6–82 months. Survivors mostly achieved a good level of physical functioning (83% in NYHA class 1–2) and adequate daily mobilization, 78% of patients. Severe depression was detected in 8% of patients (Isgro et al. 2002). The findings in a study by Schelling et al. assumed that exposure to high stress in the cardiovascular ICU can be associated with negative HRQoL outcome after cardiac surgery through traumatic memories from the immediate postoperative time. The study was prospective and evaluated a total of 148 cardiac surgical patients. HRQoL assessment was performed before the operation and compared to that by six months postoperatively (Schelling et al. 2003).

2.4.12 Redo CABG and HRQoL

Patients having redo procedures had lower HRQoL during 24 months after the operation compared to patients undergoing their first bypass surgery. A significant difference was revealed by multivariate analysis and was seen in four dimensions (energy/fatigue, health perception, physical function and role physical) of the HSQ questionnaire (Yun et al. 1999).

2.4.13 On-pump versus off-pump CABG

The method of CABG procedure and its effect on perceived HRQoL has also been object for examinations. The main finding has been that the method of operation do not affect HRQoL outcome.

In Järvinen's prospective study (Järvinen et al. 2004), 56 out of 508 operations (11%) were off-pump operations. Patients in the off-pump group were younger than in the on-pump group (57.8 years vs. 62.9 years, $p < 0.001$). On-pump patients differed significantly in comparison to off-pump patients in having more LM stenosis (22.8% vs. 7.1%, $p = 0.007$), MVD (94.5% vs. 30.3%, $p < 0.001$) and in number of bypasses performed per operation (mean 3.4 versus 1.5, $p < 0.001$). There were also slightly more women in the off-pump group ($p = 0.047$). On-pump patients had lower RAND-36 summary scores preoperatively. Both groups improved significantly in summary scores during the 12-month follow-up with a high significance ($p < 0.001$ for all domains) on all 8 dimensions of the RAND-36 measure.

A recent small randomized study of CABG surgery revealed also no HRQoL advantage for patients operated on without CPB in comparison to on-pump patients (Tully et al. 2008).

2.4.14 Impact of cardiac rehabilitation on HRQoL

Engblom et al. studied the effect of cardiac rehabilitation among elective and consecutive CABG patients for 5 years after surgery. Patients with postoperative rehabilitation reported less restriction in physical mobility than patients who did not undergo rehabilitation. They also perceived their overall health and overall life situation to be good. The difference on these two dimensions was significantly in favour of the rehabilitation group (Engblom et al. 1997).

2.4.15 Secondary prevention and HRQoL

Aggressive lowering of low-density lipoprotein (LDL) cholesterol levels has been shown to reduce the progression in saphenous vein grafts (The Post Coronary Artery Bypass Graft Trial Investigators 1997) and in the LM coronary artery (White et al. 2001). It is also associated with reduced rates of clinical events (Knatterud et al. 2000). Nevertheless a study performed by the Post CABG Study Investigators indicated that CABG patients experienced neither detrimental nor beneficial effects on HRQoL while receiving LDL-lowering therapy in doses that had demonstrable benefits on the treatment of atherosclerosis (Fox et al. 2004).

2.5 EuroSCORE and postoperative HRQoL

2.5.1 EuroSCORE risk evaluation system

The European system for cardiac operative risk evaluation score (EuroSCORE) was introduced for the stratification of operative risk of mortality for cardiac surgery (Nashef et al. 1999). It is based on a large and tightly controlled, multicentre patient database drawn from across Europe and uses logistic regression methodology to identify and give appropriate weight to various risk factors related to mortality in heart operations. EuroSCORE may have the highest predictive value for mortality and morbidity in adult cardiac surgery (Geissler et al. 2000).

In 2003 the working group introduced a logistic system in which each risk factor provides an estimate of the percent-predicted operative mortality for a patient undergoing a particular operation (Roques et al. 2003). Both additive and logistic form has demonstrated the feasibility of predicting immediate postoperative death after coronary artery bypass surgery.

EuroSCORE has also been shown to be reliable in assessing long-term survival (Toumpoulis et al. 2004). The same authors also performed another study, in which standard EuroSCORE showed very good discriminatory ability and good calibration in predicting in-hospital mortality and postoperative renal failure, and good discriminatory ability in predicting sepsis and/or endocarditis, three-month mortality, prolonged length of stay and respiratory failure. However, EuroSCORE was unable to predict other major complications, such as perioperative stroke, postoperative MI, deep sternal infection, gastrointestinal complications and re-exploration for bleeding (Toumpoulis et al. 2005). Biancari et al. confirmed the predictive role of EuroSCORE on immediate and late outcome after CABG in the

study, in which EuroSCORE was calculated for 917 CABG patients and outcome was analyzed at a median of 11.7 years later (Biancari et al. 2006).

The predictive value of EuroSCORE has also been confirmed in intensive care unit (ICU) stay and costs of adult open-heart surgery (Pinna Pintor et al. 2003, Nilsson et al. 2004).

2.5.2 EuroSCORE in predicting postoperative HRQoL

Besides predicting mortality, successful attempts have been published concerning the predictive value of risk scoring systems on overall outcome. However, only few researchers have aimed to use some risk evaluation system in predicting postoperative quality of life. EuroSCORE has so far been the only scoring for this purpose

Peric et al. studied the relationship between preoperative EuroSCORE risk prediction and postoperative HRQoL using the NHP. Preoperatively higher additive score was related to poorer HRQoL. Patients at high risk for mortality (additive EuroSCORE >6) scored lower in the sections of physical mobility and energy, as well as in total QoL. HRQoL improved significantly in all domains of NHP section 1 during 6-month follow-up. In some sections the postoperative HRQoL even approached the reference values for patient's age and gender. 85% of patients improved statistically during the 6-months follow-up, 15% deteriorated. The researchers found no significant correlation between risk scores and postoperative HRQoL in total (Peric et al. 2005). In a prospective observational study by Colak and co-workers preoperative mean SF-36 score values were significantly lower in five out of eight domains ($p < 0.001$) in the study cohort than those of the reference population. After the intervention half of the examined domains improved significantly in the study group. Patients at high preoperative risk (additive EuroSCORE > 6) improved significantly in six out of 8 domains, whereas patients at low or medium risk achieved only a slight improvement in HRQoL during 12 months postoperatively. The authors concluded that patients with high cardiac operative risk are more likely to have significant improvement postoperatively if their surgical outcome is satisfactory. SF-36 scores do not show significant changes postoperatively in patients with low and medium cardiac operative risk. Thus EuroSCORE may have predictive value for HRQoL in CABG patients (Colak et al. 2008).

El Baz with co-workers performed a study to test the association between EuroSCORE and preoperative HRQoL and, moreover, the association between EuroSCORE and gaining HRQoL at six months after CABG. The researches found that high risk EuroSCORE was associated with poor physical functioning before

the operation. By contrast EuroSCORE was not associated with mental domains preoperatively. EuroSCORE predicted perioperative complications in high-risk patients and poor self-reported physical functioning but it was not a predictor of mental functioning six months after CABG (El Baz et al. 2008).

2.6 Central nervous system disorders associated with CABG

2.6.1 General considerations

Advances in surgical and anesthetic techniques have made it possible to offer surgical interventions to patients in older ages and with more co-morbidity. Although overall operative mortality has decreased, the potential risk for neurological injury has become greater. Neurological damage including delirium remains a concern for elderly patients undergoing cardiac surgery.

Central nervous system (CNS) complications caused 7.2% of all deaths after cardiac surgery in the 1970s. Later it rose to almost 20% by the mid-1980s (Wolman et al. 1999). Cognitive decline occurred in as many as 80% of patients immediately after surgery and still in 30% by 6 months (Selnes et al. 1999). Delirium and other neurological disorders are also associated with increased morbidity and mortality, as well as prolonged hospital stays. Compared to patients with no adverse outcomes, patients with diagnosed delirium had up to 5 times higher mortality, 2 to 4 times the time spent in intensive care and in the hospital and 3 to 6 times the need for prolonged care (Roach et al. 1996, Wolman et al. 1999, Bucerius et al. 2004, Newman et al. 2004, Newman et al. 2006). Moreover, adverse neurological outcome restricts the improved HRQoL that patients usually experience after heart surgery (Newman et al. 2006).

2.6.2 Definition of postoperative neurological disorders

Adverse neurological outcome is divided into two categories. Type I neurological disorder is associated with focal brain injury i.e. stroke, or stupor or coma at discharge. Type II disorder is defined as deterioration in intellectual function, confusion, agitation, disorientation, memory deficit or seizures without evidence of focal injury (Roach et al. 1996).

2.6.3 Definition and diagnostic criteria of delirium

The word “delirium” derives from the Latin *delirare*, which means, “to be out of one’s furrow” (Fricchione et al. 2008).

Diagnosis of delirium is based on the fulfilment of criteria that include acute onset and fluctuating course, inattention, delusions, confusion, and cerebral excitement or altered level of consciousness of comparatively short duration (Inouye et al. 1990, Inouye et al. 1993). Bucerius and co-workers defined postoperative delirium as a transient mental syndrome of acute onset characterized by global impairment of cognitive functions, a reduced level of consciousness, attention abnormalities, increased or decreased psychomotor activity and disordered sleep-awake cycle (Bucerius et al. 2004). A descriptive feature for delirium is agitation, which often occurs in the context of delirium. It can be defined as excessive motor or verbal behaviour that interferes with patient care, patient or staff safety and medical therapies. Examples in hospitalized patients include excess motor activity, aggressiveness, shouting, fighting, scratching, pulling out tubes and monitoring devices and climbing out of bed (Sockalingam et al. 2005).

The diagnostic criteria for delirium can be summarized as follows (Brown et al. 2002, Fricchione et al. 2008):

1. Disturbance in consciousness with reduced ability to focus, sustain or shift attention.
2. Change in cognition (memory, speech, disorientation, and disturbance) or development of perceptual disturbance not better accounted for by pre-existing or evolving dementia.
3. Disturbance develops over hours to days and fluctuates in severity.

2.6.4 Incidence of delirium in hospitalized patients

The incidence of delirium is 10-30% in hospitalized medically ill patients (Brown et al. 2002). Among elderly patients it occurs in 14%–56%, thus being the most frequent complication of hospitalization in this population (Inouye et al. 1993).

In abdominal aortic aneurysm (AAA) repair the incidence of delirium has been observed to be 41–53% (Marcantonio et al. 1994) and in peripheral vascular surgery up to 48% (Böhner et al. 2003). Generally, surgical procedures with so high a risk for delirium such as CABG, AAA repair and peripheral vascular surgery are performed on patients with a high burden of generalized atherosclerosis. This means that

patients needing coronary artery surgery are likely to have subclinical or clinical atherosclerosis also in non-cardiac vascular beds (Figure 4).

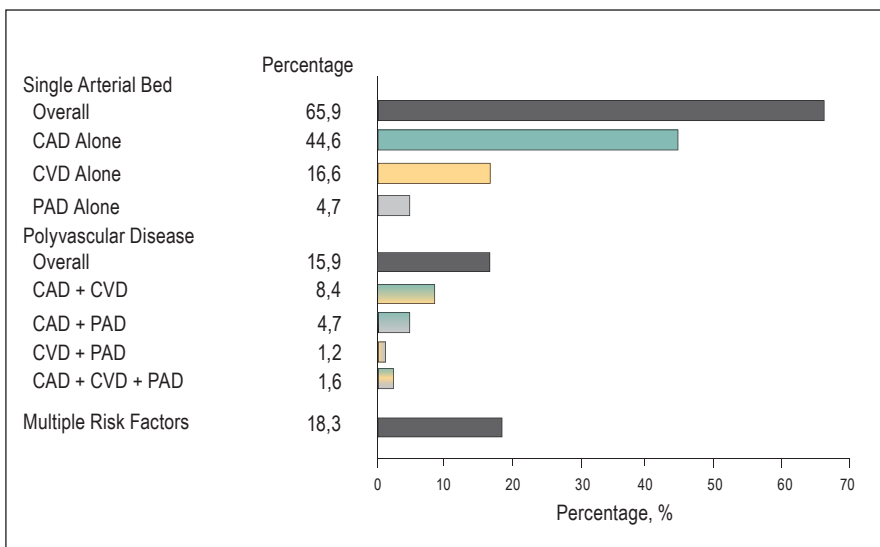


FIGURE 4. Distribution of the three main manifestations (CAD, coronary artery disease; CVD, cerebral vascular disease; PAD, peripheral vascular disease) of atherosclerosis. Modified from Bhatt et al. 2006.

In contrast, lower incidences of postoperative delirium have been reported concerning nonvascular surgical procedures such as elective orthopedic surgery or non-emergent abdominal surgery (9–15%) (Marcantonio et al. 1994, Galanakis et al. 2001), gastrointestinal surgery in elderly patients (5–26%) (Marcantonio et al. 1994, Kaneko et al. 1997) and 35–65% following operative treatment for hip fracture (Gustafson et al. 1988, Marcantonio et al. 2001). Postoperative cognitive dysfunction likening that seen in cardiac surgery was present in 25.8% (95% CI 23.1–28.5) of patients one week after surgery and in 9.9% (CI 8.1–12.0) of patients three months after surgery. Risk factors were increasing age and duration of anesthesia, a second operation and postoperative complications, i.e. reoperations, infections and respiratory complications (Moller et al. 1998).

2.6.5 Incidence of delirium in cardiac surgery

The reported incidence of delirium after cardiac surgery ranges from 3% to 47% depending on the type of procedure performed (van der Mast et al. 2000). Studies from the 1980s have demonstrated that as many as 32 to 73% of patients developed

delirium after CABG (Hammeke et al. 1988, Smith et al. 1989, Dyer et al. 1995). A prospective, observational multicentre study performed by Roach et al. (1996) included a total of 2,108 patients undergoing CABG. Type II outcomes occurred in 3.0%. In Wolman's prospective multicentre study from 1999 the incidence of Type II neurological disorder was 7.3%. According to Georgiadis et al. (2000) the incidence of delirium was 13.7% in mixed patient material of CABG and valve patients, whilst van der Mast et al. (1999) reported an incidence of 13.5% in CABG patients. In a small study reported by Rolfson the incidence of postoperative delirium after CABG was as high as 32% (Rolfson et al. 1999). Giltay et al. (2006) reported the rate of severe psychotic symptoms in 2.1% of open-heart operations in a study that evaluated a total of 8,139 patients in a single centre. Thus, delirium is common after cardiac surgery, particularly among older patients, but is often under-diagnosed (Eriksson et al. 2002).

The incidence of delirium is lower in studies based on clinical diagnosis (Bucerius et al. 2004) than in those with structured interviews. In a prospective study by Eriksson and co-workers the Organic Brain Syndrome measure evaluated CABG patients prospectively. The incidence of delirium was 23%. One fourth of delirious patients were classified to have actual psychotic delirium while 58% had hallucinations (Eriksson et al. 2002). Isolated bypass surgery patients may have a lower risk when compared with valve surgery patients.

2.6.6 Predictive factors of postoperative delirium

Several causes of postoperative delirium can be distinguished. While among non-cardiac surgical patients metabolic causes, infections and vascular disorders are the most common reasons (Brown et al. 2002), adverse neurological outcome in cardiac surgery is associated for the most with aortic and cerebrovascular atherosclerosis and embolization. Predisposing factors for postoperative delirium associated with cardiac surgery are listed in Table 2.

TABLE 2. Predictive factors of postoperative delirium in cardiac surgery.

Variable	Reference
Age	Roach et al. (1996), Bucerius et al. (2004), Giltay et al. (2006)
Atherosclerosis of aorta and carotid vessels	
Proximal aortic atherosclerosis	Wolman et al. (1999), Newman et al. (2001), Rudolph et al. (2005, 2006)
Carotid artery stenosis	Bucerius et al. (2004), Ho et al. (2004), Rudolph et al. (2005, 2006)
Previous cerebral injury	
History of stroke	Goto et al. (2001), McKhann et al. (2006)
Redo bypass surgery	Roach et al. (1996)
Combined bypass and valve operation	Wolman et al. (1999)
Lowered LVEF	Bucerius et al. (2004), Giltay et al. (2006)
Cardiopulmonary bypass	Murkin (1995), Murkin (2006)
Embolization	Pugsley et al. (1994), Borger et al. (2001), Abu-Omar et al. (2004)
Temperature	Martin et al. (1994)
Neurotransmitters	van der Mast (1999)
Systemic inflammatory response	Westaby et al. (2001), Hindman (2002).
Intracardiac procedures	
Aortic or mitral valve reconstructions	Wolman et al. (1999)
Endocarditis	Wolman et al. (1999)
Urgency of the operation	Bucerius et al. (2004)
Prolonged operation time	Bucerius et al. (2004)
Perfusion time	
Aortic x-clamp time	
Excessive red blood cell transfusion	Bucerius et al. (2004)
Low-output conditions	Wolman et al. (1999)
Postoperative infections	Giltay et al. (2006)
Atrial fibrillation	Clark et al. (1995), Borger et al. (2001), Stanley et al. (2002)
Hypertension	Roach et al. (1996), Wolman et al. (1999)
COPD	Roach et al. (1996), Giltay et al. (2006)
Diabetes	Bucerius et al. (2004)
Renal insufficiency	Giltay et al. (2006)
Peripheral vascular disease	Bucerius et al. (2004), Ho et al. (2004)
Excessive alcohol consumption	Roach et al. (1996), Wolman et al. (1999)

2.6.6.1 Age and postoperative delirium

There is no uniform correlation between age and postoperative delirium related to CABG, but elderly patients tend to develop delirium at a higher rate (Dubin et al. 1979). Later references confirm the predicting role of advanced age on postoperative delirium.

Roach and co-authors reported, that advanced age, particularly 70 or over, was an important factor both for Type I and Type II outcome and the incidence of them grew almost exponentially with increasing age as seen in Figure 5. Adjusted OR for Type II complication was 2.20 (95% CI 1.60–3.02, $p < 0.05$) per additional decade.

The finding was confirmed by Bucarius et al. in a prospective study on 16,184 patients undergoing cardiac surgery. In this study prevalence of delirium was 11.9% among CABG patients with CPB over 70 years. BH surgery and younger patient age (<70 years) were associated with lower risk of delirium (Bucarius et al. 2004). Also in a large single-centre study performed by Giltay and co-authors was found that high age (≥ 70 years) (OR 5.1, 95% CI 2.8–9.2) was an independent preoperative predisposing factor for postoperative delirium in a multivariate logistic model.

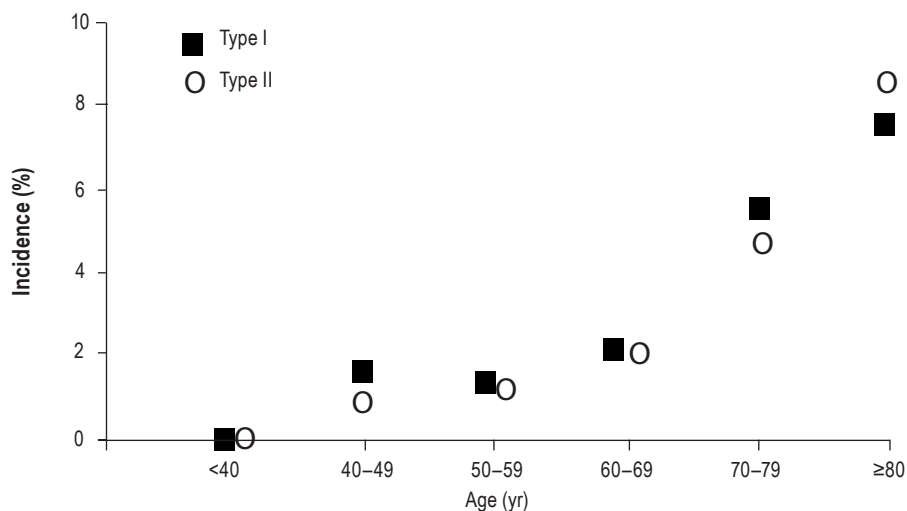


FIGURE 5. Incidence of Type I and Type II neurological outcomes according to age after CABG. Modified from Roach et al. 1996.

2.6.6.2 Atherosclerosis of aorta and carotid vessels

Rudolph and co-workers studied prospectively, whether atherosclerosis of the ascending aorta, internal carotid arteries and coronary arteries is predictive of postoperative delirium in CABG surgery. The incidence of delirium was 41.7%. In bivariate analysis carotid artery stenosis $>50\%$ (RR 3.5, 95% CI 1.5–8.1) and moderate or severe ascending aortic atherosclerosis (RR 2.9, 95% CI 1.0–8.5) were significantly associated with the development of delirium (Rudolph et al. 2005, Rudolph et al. 2006). This finding confirms those reported by Bucarius et al. (2004). Also in Wolman's study proximal atherosclerosis of the aorta strongly predicted postoperative delirium (OR 6.5, 95% CI 1.8–22.6) (Wolman et al. 1999) and Ho and co-authors emphasized both CVD and PVD as predictors of neurocognitive decline after CABG (Ho et al. 2004). Surprisingly, in the report by Roach et al. (1996) proximal aortic atherosclerosis did not predict postoperative delirium. A

history of cerebrovascular disease may indicate atherosclerosis also within the cerebrovascular system and particularly of the carotid arteries, which may act as source of embolization. The same concerns also manipulation of the aorta (Newman et al. 2001).

2.6.6.3 Previous cerebral injury

Novel examinations of the brain show, that elderly patients referred for CABG may have silent brain infarcts even preoperatively. In a large study by Goto and colleagues 30% of CABG patients had small brain infarctions before the operation detected in magnetic resonance imaging (MRI). In 20% of patients even multiple infarctions were detected. 7% of patients without apparent brain infarctions had postoperative neuropsychological dysfunction, whereas patients with small infarctions and with multiple infarctions had neuropsychological dysfunction rates of 13% and 20% respectively. Multiple infarctions significantly increased the risk of neurological dysfunction after CABG. The findings suggest that the probability for neurological injury seen after operation is connected with the severity of pre-existing atherosclerotic disease and with the amount of preoperative cognitive and neurological reserve (Goto et al. 2001).

2.6.6.4 Cardiopulmonary bypass and cerebral embolization

CPB may cause neurological dysfunction secondary to intraoperative cerebral embolization. Pugsley et al. examined the incidence of high-intensity transcranial signals (microemboli) and their relation to neuropsychological performance after surgery using transcranial Doppler (TCD). Data were available on 100 consecutive patients undergoing routine CPB. Fifty of the patients were randomly assigned to have a 40-micron arterial line filter. More high-intensity signals were detected with TCD in the group without arterial line filtration and significantly more patients were detected to have neuropsychological defects in this group at 8 days ($p < 0.05$) and at 8 weeks ($p < 0.03$) than in the group with filtration (Pugsley et al. 1994). Abu-Omar and co-researchers detected a seven-fold increase in microemboli in on-pump procedures compared with the off-pump group. Moreover, solid microemboli, which are suggested to be more damaging, were significantly reduced in the off-pump group (Abu-Omar et al. 2004). Increasing duration of CPB was associated with an increasing embolic load of the brain (Hammon et al. 1997, Brown et al. 2000).

TCD and carotid ultrasonography (carotid duplex doppler, CDD) have shown high rates of cerebral emboli, especially during aortic interventions, including aortic cannulation or aortic cross-clamp. However, the correlation between neurological injury and aortic atherosclerosis may be more reliable when measured

by transesophageal echo cardiography (TEE) or epiaortic ultrasonography imaging. Gaseous embolization is also possible during the CPB (Borger et al. 2001). However, distinguishing less harmful air emboli from the more dangerous particulate emboli may be difficult (Newman et al. 2006).

Small capillary arteriolar dilations in the brain are the result of microembolization of lipids or other substances that could cause perioperative neurological injury. This finding has been discussed in combination with post-mortem studies on brains (Challa et al. 1993). MRI studies have recorded that up to 45% of patients will have brain lesions after CABG or aortic surgery (Friday et al. 2005; Bar-Yosef et al. 2004). However, such injury has not been directly linked to neurocognitive decline.

2.6.6.5 Cardiopulmonary bypass temperature

The usual practice is to allow the temperature to drift during “normothermic” CPB with temperatures reaching 34°C or lower. A single study comparing true normothermia with hypothermia during CPB showed a significantly greater incidence of focal neurologic injury in the warm CPB group. The finding supports the role of hypothermia in cerebral protection and as a potential predictor variable for cognitive decline (Martin et al. 1994). However, the finding of McLean and co-workers was opposite and authors did not find any difference in focal neurologic deficit or cognitive decline between warm and moderately hypothermic groups (McLean et al. 1994). Also the effect of CPB on neurotransmitters, including serotonergic, noradrenergic, dopaminergic and anticholinergic systems may be a contributing factor causing delirium (van der Mast 1999).

CPB is associated with a profound systemic inflammatory response, which might contribute to postoperative neurological and neuropsychological damage (Hindman 2002). However, the inflammatory response alone may not be the sole causative factor of adverse neurological outcome. Westaby also found no significant association between inflammatory markers and neurocognitive injury. Inflammation is probably a contributory factor, not a causal one (Westaby et al. 2001).

2.6.6.6 Atrial fibrillation and cerebral embolization

The role of postoperative atrial fibrillation (AF) on neurocognitive outcome after CABG has been also an object of investigation. AF is a commonly seen condition after CABG with an incidence of 20% to 40% (Mathew et al. 1996, Halonen et al. 2007). One of the most disturbing complications associated with AF may be stroke (Lahtinen et al. 2004). Atrial fibrillation is widely recognized associated with cerebral embolization and postoperative neurobehavioral deficits (Clark et al. 1995, Borger

et al. 2001). Stanley et al. in a prospective study investigated the association between postoperative AF and neurocognitive decline after CABG and found that frequency of AF was 22%. Patients who developed AF showed more cognitive decline than those who did not ($p=0.036$). The mechanism is postulated to relate to an increased risk of cerebral embolization or hypoperfusion caused by a reduced cardiac output state (Stanley et al. 2002).

2.6.6.7 Preoperative depression

Preoperative depression has been shown to have effect on postoperative outcome after coronary artery surgery. Blumenthal et al. showed that preoperative moderate to severe depression or postsurgical onset depression increased the risk of death to twice that of non-depressed patients from 3–4 years after the operation onwards in a mean follow up of 5.2 years (Blumenthal et al. 2003). Although depression has not been proving to be a major factor to neurocognitive disorder caused by cardiac surgery, depressed patients report more subjective complaints about their memory and other cognitive abilities than non-depressed patients (McKhann et al. 1997).

2.6.7 Beating heart surgery and neurological outcome

The advance of OPCAB in the prevention of neurological or neurocognitive injury is controversial. Preliminary data suggest that there is less cognitive decline and stroke associated with off-pump surgery (Iglesias et al. 2001). Bucarius et al. (2004) observed also that beating heart (BH) surgery had a beneficial effect on adverse neurological outcomes in cardiac surgery (OR 0.14).

In BH surgery the leading conception is to avoid the adverse effects of CPB, i.e. hypotensive periods, nonpulsative blood flow and gaseous and/or particulate embolization. The avoidance of ascending aortic manipulation or cannulation may also reduce subsequent risk of atherosclerotic embolization (Murkin et al. 1999, Bucarius et al. 2004). In a large randomized trial to compare off-pump with on-pump CABG van Dijk and co-authors found that there was less cognitive decline shortly after OPCAB operation but no substantial difference between groups after 1 year (van Dijk et al. 2002). There also remains concern as OPCAB is associated with incomplete revascularization. Thus, high risk patients might accept a compromise, OPCAB, to prevent adverse neurological events, whereas patients with lower risk profile and younger age are directed to have conventional CABG to increase the chances of more complete revascularization and longer graft patency (Puskas et al. 2004).

In a well-designed study Hernandez et al. compared two patient groups, which underwent conventional CABG or OPCAB surgery. The researchers found no difference in neurocognitive deficit at discharge (RR 0.83, 95% CI 0.65–1.07) or at 6 months (0.94, 95% CI 0.70–1.28). The conclusion was, that off-pump surgery did not result in decreased frequency of neurocognitive decline. However, the study was not fully blind and in addition, the sample size calculation was based on achieving a one-third reduction in cognitive dysfunction in the OPCAB group (Hernandez et al. 2007).

In a recent study Selnes and co-authors compared changes in cognitive performance from preoperative baseline to 3 years in patients undergoing on-pump CABG with those of three control groups: patients undergoing OPCAB surgery, patients with diagnosed coronary artery disease but no surgery and those without CAD risk factors. The main finding was that there was a non-significant trend toward late postoperative cognitive decline for all study groups with CAD. On-pump and off-pump patients did not differ in terms of late postoperative decline. All patients with coronary artery disease had substantially lower cognitive test performance even before surgery. Therefore postoperative differences cannot be attributed to the surgical intervention or CPB (Selnes et al. 2007).

Surgical technique seems also to be very important factor in determining neurological outcome. In a prospective randomized study CABG patients were assigned to multiple aortic cross-clamp, single aortic cross-clamp and off-pump groups. At 6 months 26% of multiple aortic cross-clamp patients and 27% of off-pump patients had neuropsychological deficits whereas only 9% of single aortic-clamp patients had similar problems ($p=0.067$). OR for multiple aortic cross-clamp versus single clamp technique was 3.7 and for OPCAB versus single cross clamp 3.5. Carefully performed aortic cross-clamp and minimal aortic manipulation may be equal or even superior to BH surgery in avoiding neuropsychological disorders related to CABG. However, the finding did not reach statistical significance in this very small patient material (Hammon et al. 2007).

2.6.8 PCI and delirium

Studies comparing CABG and PCI have failed to show a substantial difference in neurocognitive decline. Percutaneous revascularization offers at least theoretically a chance of achieving equivalent coronary revascularization with fewer traumas when compared to CABG. Further, catheter based technology allows also older patients to undergo coronary artery revascularization. PCI patients would be likely

to show a difference in neurological outcomes if procedural factors are the major contributor to such complications (Newman et al. 2004). The BARI study did not reveal any difference in long-term cognitive function between CABG and PTCA patients (Hlatky et al. 1997, Hlatky et al. 2004). Similarly, a substudy of the SoS Trial could not demonstrate a significant difference in neuropsychological outcome in patients treated with different revascularization techniques (Währborg et al. 2004).

2.6.9 Neurocognitive decline and time in cardiac surgery

Delirium has comparatively short and temporary duration (Inouye et al. 1990, Inouye et al. 1993) and most of the cognitive changes after cardiac surgery are transient with resolution occurring within 6 weeks to 6 months in more than half of the affected patients (Newman et al. 2001). However, Sotaniemi et al. found that perioperative level of cognitive functioning predicted a higher degree of persistent dysfunction at 2 months, 1 year and even 5 years postoperatively (Sotaniemi et al. 1986, Sotaniemi 1995). Selnes et al. later confirmed this result (Selnes et al. 2001). A major limitation of studies on defining cognitive change after CABG is that most of them do not compare the incidence of postoperative cognitive decline among CABG patients to that observed in a control group, i.e. either healthy persons or those with similar degrees of cardiovascular and cerebrovascular disease. In fact, in the absence of a control group the criterion for cognitive decline is based on an arbitrary measure of change within the study population (McKhann et al. 1997, Selnes et al. 2006). Thus, using nonsurgical patients as control Selnes et al. concluded that previously reported late cognitive decline after CABG may not be specific to the use of CPB, but may occur in patients with similar risk factors of cardiovascular and cerebral vascular disease (Selnes et al. 2005).

3 AIMS OF THE STUDY

The aims of the present study were:

1. to investigate HRQoL in patients undergoing CABG (I)
2. to define the effect of postoperative delirium or confusion on HRQoL after CABG (II)
3. to investigate the role of a risk scoring system (EuroSCORE) in predicting postoperative HRQoL in CABG patients (III)
4. to examine development of HRQoL and change in symptoms and in performance capacity after the two options for invasive treatment of coronary artery disease, either CABG or PCI, during a long-term follow-up of 36 months (IV)
5. to define the need for repeat invasive treatment after initial PCI or CABG over a lengthy period (V)

4 PATIENT MATERIAL AND METHODS

The study was carried out between October 1, 2000 and January 31, 2003 at the Department of Thoracic and Cardiovascular Surgery and the Department of Cardiology, Vaasa Central Hospital (VCH), Vaasa, Finland. VCH is one of the 20 central hospitals in Finland. It provides invasive cardiological (coronary angiography, PCI) and adult open-heart surgery services for a population of 166,000 inhabitants and partly for an adjacent region with 195,000 inhabitants. The annual number of coronary angiographies performed has been 1,000–1,100. The frequency of PCI has grown throughout years up to some 400 procedures per year. The use of stents has followed the general development and trends in catheter-based treatments. The number of CABG stabilized on a level of 250–280 per year. Over 90% of operations have been performed conventionally using CPB.

4.1 Patients and study designs

4.1.1 Patient selection

The patient material consisted of a sample of patients referred for coronary artery angiography to VCH. The patients were asked to participate voluntarily in a study to investigate their HRQoL for three years after the angiography and invasive treatment. Some of the patients were referred for angiography due to undue fatigue or dyspnoea resulting in limitation of physical activity and a minority of patients were to undergo some major and high-risk operation, i.e. reconstruction of (AAA) and coronary artery evaluation was performed in order to minimize the operative risks.

The referred patients had been evaluated for ischemic heart disease by an internist or cardiologist and most of them had undergone not only an exercise test

but also echocardiography in aim to reveal the functional state of the left ventricle (ejection fraction, EF) and the function of the heart valves. However, patients were not optimized for the pre-treatment medication, although they were usually treated with anti-ischemic, anti-thrombotic (acetosalisylic acid) and with cholesterol lowering medicines.

On their first visit to the cardiology unit the patients were asked – before coronary angiography – to participate voluntarily in a study for HRQoL. The research nurse then interviewed elective patients at the cardiological unit. Thus the main criteria for patient selection were the impending invasive examination together with voluntariness for the follow-up study. Patients undergoing coronary angiography and operated on as emergencies were interviewed on the ward after angiography but before surgery. In total 1,330 patients consented and were included in the follow-up. As seen in the patient flow chart (Figure 6) a total of 662 patients undergoing either CABG or PCI were included in the present study and analyzed for outcome and for changes in self-assessed HRQoL.

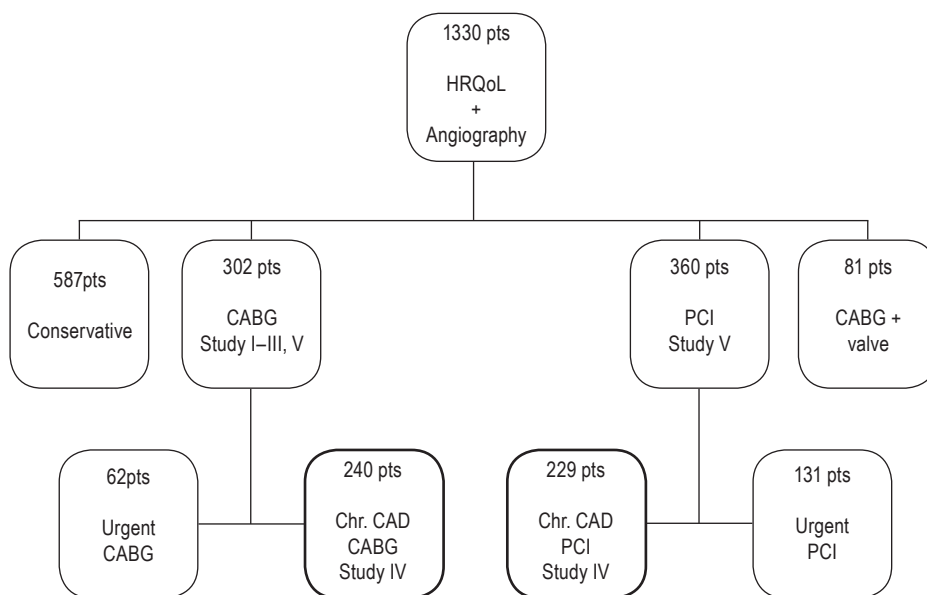


FIGURE 6. Flow chart and formation of patient groups according to the findings of angiography.

4.1.2 Determinations of HRQoL

The first interview was performed in order to elicit the basic HRQoL of patients. A Finnish or Swedish form of the 15D was used depending on the patient's native language. All patients included were assessed with follow-up questionnaires, which were mailed 6 months and 18 months after CABG or PCI. The research nurse personally interviewed surviving patients at a follow-up visit after 36 months (Figure 7). The last control interview also included questions on physical performance, symptoms of angina, contentment and medication at the time. The research nurse completed each patient's data of health care visits or hospital treatments during the 36-month follow-up. The follow-up finished at the end of January 2006.

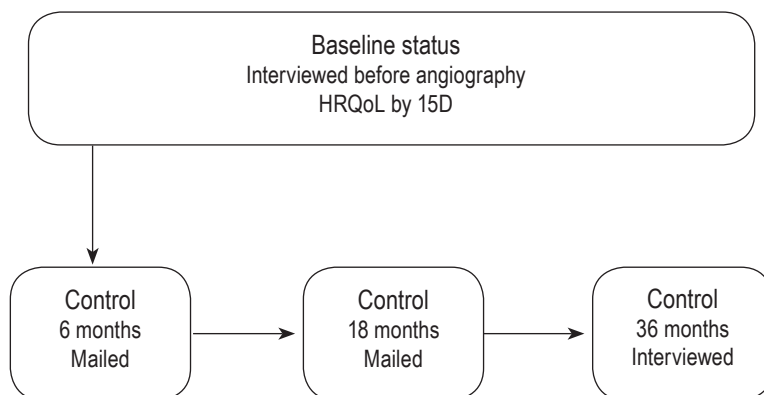


FIGURE 7. Design of the study course.

4.1.3 Design of the study

The study was designed as a prospective clinical and observational trial. Inclusion of patients was not completely consecutive due to patient overflow for the research nurse and due to refusals. The recruitment of patients was also discontinued during the holiday periods and other free times of the research nurse. Selection of treatment method was based on angiographic findings and clinical decision-making. The treatment option was not random but rather from the real world practice. HRQoL was followed up prospectively in each patient and each study group.

4.1.4 Preoperative and perioperative data

Demographic and perioperative data of the CABG patients and the PCI patients are presented in Table 3. Data were collected prospectively in an institutional cardiological and surgical computerized database (Summit Vista®, Summit Medical Systems, Inc., Minnetonka, USA), which included information about risk factors, admission, procedure, discharge dates and discharge status of patients, but also findings of repeat angiograms or interventions. Pre-procedural variables were reported according to the Society of Thoracic Surgeons (STS) (Edwards et al. 1994) and EuroSCORE (Nashef et al. 1999) definitions. Both additive and logistic risk of mortality was calculated for each patient undergoing CABG (Roques et al. 2003). Survival analysis was based on the Finnish nationwide population registry.

TABLE 3. Baseline characteristics of the patients, univariate analysis.

Characteristics	CABG (n = 302) %	PCI (n = 360) %	P-value
<i>Demographic characteristics</i>			
Age, years (SD) [range]	66.3 (9.0) [44.1– 84.5]	64.5 (10.1) [37.6– 86.8]	0.019
Age (% of patients)			
< 65 yr	38.7	47.8	0.065
65–74 yr	42.7	36.4	
> 75 yr	18.5	15.8	
Sex (% of patients)			
Male	79.1	70.6	0.007
<i>Common risk factors for CAD</i>			
Diabetes	25.5	18.1	0.023
Hypercholesterolemia	70.9	61.7	0.014
Hypertension	56.3	57.2	0.814
<i>Coexisting conditions</i>			
Chronic pulmonary disease	9.9	10.3	0.898
Extracardiac arteriopathy	11.3	7.8	0.141
Previous cardiac surgery	3.3	7.2	0.038
Previous PCI	5.0	8.3	0.058
Urgency	20.5	36.1	0.001
Recent myocardial infarction	37.7	35.8	0.628
1–7 days	5.0	15.6	<0.001
> 8 days	32.8	20.3	<0.001
NYHA Class 1	1.7	8.1	<0.001
NYHA Class 2	36.4	30.0	0.097
NYHA Class 3	43.7	34.7	0.025
NYHA Class 4	18.2	26.7	0.006

Heart related factors

No. of diseased vessels			
1 VD	5.6	52.2	<0.001
2 VD	28.5	33.3	0.206
3 VD	65.9	14.4	<0.001
LMCA >50 %	32.5	1.9	<0.001
LVEF			
< 30 %	3.3	2.8	1.000
30–50 %	43.0	19.4	<0.001
>50 %	53.0	59.7	<0.001
Data missing	0.7	18.1	<0.001

4.1.5 Reference population

In Study I the baseline status of the HRQoL of the CABG patient group was compared with a sample of 4,111 age- and sex-matched people from the Health 2000 project of the Finnish National Public Health Institute. Health 2000 was a health interview/examination survey carried out in Finland from fall 2000 to spring 2001, in which the 15D instrument was used to assess HRQoL among a total of 6,166 individuals (<http://www.ktl.fi/health2000/index.uk.html>).

In Study IV we compared the 36-month 15D profile of the study cohort with the profile of a sample of 4,603 age- and sex-matched people from the aforementioned project.

4.2 Measuring of HRQoL

4.2.1 The 15D instrument

The present study was officially registered to use the 15D as instrument for assessing HRQoL. The 15D is a generic (non-disease-specific), comprehensive, multidimensional, standardized and self-administered measure, which can be used both as a profile and single index score measure (Sintonen 2001). It describes health status along 15 dimensions: mobility, vision, hearing, breathing, sleeping, eating, speech, elimination, usual activities, mental function, discomfort and symptoms, depression, distress, vitality and sexual activity (Appendices 3, 4 and 5).

Each dimension comprises five response options. Each of the five points of the ordinal scale is presented as a statement about that particular health dimension. The statements move in order from full function to minimal or no function for

that health dimension. Lower values indicate better functioning. A second valuation phase of weighting health preferences for the general population leads to a single index score. The single index score, 15D score on a 0–1 scale, represents overall HRQoL, and is calculated from the health state descriptive system using a set of population-based preference or utility weights. The maximum score is 1 (no problems on any dimensions) and the minimum score 0 (being dead). If a patient left one or two questions out of fifteen unanswered, the missing data were derived and replaced according to 15D instructions (<http://www.15d-instrument.net/rmd>) (Sintonen 1994).

The 15D scores have proved highly reliable, sensitive and responsive to treatment related change. The instrument has been tested in various states of illness (Haapaniemi et al. 1995, Malmivaara et al. 1995, Kauppinen et al. 1998), also concerning invasive treatment of CAD (Kattainen et al. 2005, Elliott et al. 2006). The benefits of the 15D are in its face validity, range of dimensions, brevity and ease of completion because of the standard response format. As a profile measure the 15D performs equally well with the NHP and clearly better on roughly comparable dimension than EQ-5D. Although it is also possible to get an index score by using RAND-36, the capability of the measure to distinguish change in low index values is quite poor (Sintonen, personal information 2009). Moreover, besides of nearly comparable dimensions the 15D has still 9–10 more adjunctive dimensions than other measures, which provide a large reserve in terms of discriminatory power and responsiveness to change. The 15D also has a large and recent reference population from the Finnish Health 2000 Survey allowing tailor made comparisons between patients and age- and sex-matched individuals.

The most significant weakness in using this measure is its rather poor recognition in the literature and among researchers, although the form of the instrument has been translated into over 15 languages. Thus we are not able to make direct comparisons between different surveys, although trends in changes of HRQoL may be similar from one measure to another.

4.2.2 Clinically relevant change in HRQoL

The minimum clinically and practically important change in the 15D score which the patients on average can feel as a change was defined as ≥ 0.03 or ≤ -0.03 , correspondingly (Sintonen 1994, Sintonen 2001).

4.3 Other determinations

4.3.1 Physical performance state

Physical performance was defined according to the New York Heart Association (NYHA) classification and recorded both preoperatively and at the follow-up visit after 36 months. We used STS definitions whereby angina as a symptom was included in the NYHA classification. Thus we did not report patients' symptoms according to the Canadian Cardiovascular Society (CCS) classification (Campeau 1976), which deals more with pure chest pain as a symptom. Physical performance capacity was based on patients' own opinion and no objective performance tests were implemented.

4.3.2 Significant narrowing of coronary lesions

Lesions with stenosis of more than 50% of the luminal diameter in a coronary artery were considered significant on the diagnostic angiogram. The cardiologist usually opted for PCI with the patient's concurrence whereas cardiologists and cardiac surgeons always discussed the decision for CABG. Four cardiologists performed PCI and three cardiac surgeons performed all bypass operations. Coronary stenting used a stent available on perception of lesion requirements.

4.3.3 CABG technique

Of the operations 93.3% were conventional CABG in which CPB was performed using a membrane oxygenator and an arterial line filter. 6.7% of operations were performed off-pump. During the study period epiaortic ultrasound imaging was not available. Single-clamp technique was used in performing proximal anastomoses. Myocardial protection was ensured with continuous retrograde blood cardioplegia combined with antegrade infusion into grafts. A median of 4 (range 1–7) anastomoses was performed surgically.

4.3.4 PCI technique

Four cardiologists performed all angiographies and PCI treatments. Coronary stenting was performed with a stent available on perception of lesion requirements. The median number of coronary artery lesions treated by PCI was 1 (range 1–3). Coronary stenting was used in 87% of procedures and almost all used stents were BMSs.

4.3.5 Postoperative follow-up

CABG patients with uncomplicated course usually visited cardiologist or internist 1–2 months after discharge from hospital but thereafter controls were transferred to primary health care. Uncomplicated PCI patients were controlled only in health centers. In more complicated cases patient controls continued in the cardiological outpatients' unit. Both CABG and PCI patients had a voluntary but not routine opportunity to participate in a heart rehabilitation program towards the end of the first postoperative year. The extent of rehabilitation of invasive cardiac patients was not evaluated in association with the present study.

4.4 Statistical methods

Statistical analyses were performed using SPSS 14.0 for Windows. Patient-related and postoperative outcome variables are presented as percentages. Continuous variables are reported as mean \pm standard deviation (SD) or as median [range]. Baseline and follow-up variables were compared using Pearson's Chi-Square Test or Fisher's Exact Test. Mann-Whitney or Kruskal-Wallis test compared continuous variables with non-normal distributions. Analysis of variance (ANOVA) was used for repeated measurements. In Study II binary logistic regression (forward stepwise method) was carried out to assess the factors associated with postoperative delirium. In Study III Spearman's test and Receiver Operating Characteristics (ROC) curve was used to estimate the predictive value of the additive assessed correlation between continuous variables and logistic EuroSCOREs for any significant increase on 15D score as defined by ≥ 0.03 over the preoperative score. Cox regression analysis was used to estimate the relative risk of repeat revascularization in Study V. Cumulative survival was calculated using the Kaplan-Meier method and the log-rank test was

used to compare survival between patient groups. The level of statistical significance was set at <0.05 .

4.5 Ethical aspects

The Ethics Committee of Vaasa Central Hospital District approved the study. Written informed consent was obtained from each patient at the time of the primary interview.

4.6 Material and methodological considerations of the individual studies

4.6.1 Study I

In this study we aimed at determining changes in HRQoL for CABG patients in a mid-term (18-month) follow-up. A total of 302 patients (239 male and 63 female) were included. In the age group <65 yrs there were 117 patients, in the age group 65–74 yrs 129 patients and in the oldest group (> 75 yrs) 56 patients. Demographics and preoperative data of the patients are given in Table 4.

TABLE 4. Preoperative data of CABG patients ($n = 302$) and of the three age groups.

Variable	Sample %	< 65 yrs %	65–74 yrs %	> 75 yrs %
Male gender	79.1	86.3	77.5	67.9
Age, years, mean (SD)	66.3 (9.0)	56.9 (5.3)	68.5 (2.7)	78.3 (2.4)
NYHA				
Class 1	1.7	0.9	2.3	1.8
Class 2	36.4	41.9	36.4	25.0
Class 3	43.7	41.9	41.9	51.8
Class 4	18.2	15.4	19.4	21.3
ASA Class 4	43.7	23.1	44.2	85.7
3-vessel disease	85.4	82.9	85.3	91.1
LM stenosis > 50 %	33.4	26.5	34.9	50.0
Additive EuroSCORE, mean (SD)	3.3 (2.4)	1.5 (1.4)	3.8 (1.6)	6.4 (2.1)
Logistic EuroSCORE, mean (SD)	3.5 (4.1)	1.6 (1.0)	3.4 (2.5)	7.6 (7.1)
Diabetes	25.5	24.8	24.0	30.4
Hyperlipidaemia	70.9	79.5	65.1	66.1
Hypertension	56.3	61.5	53.5	51.8
CVD	8.3	0.9	11.6	16.1
CHF	3.6	0.9	6.2	3.6
Obesity ¹	24.8	25.6	23.3	25.0

¹ BMI ≥ 30

A total of 553 CABG operations were performed during the study period. Thus 251 CABG patients were missed. The reason was usually overflow of daily questionnaires to be performed by a single research nurse but also due to prescribed vacations of research personnel. Refusals were very seldom. The patients, who were not included in the study (n=251), were more often female (31.5% vs. 20.9%, $p=0.004$) and older (mean age 68.9 vs. 66.3 yrs, $p=0.002$). They were operated on more often as emergencies (12.4% vs. 1.3%, $p<0.001$) and had a higher additive EuroSCORE (mean 5.3 vs. 3.4, $p<0.001$).

After six months 97.7% of surviving patients returned the questionnaire, and after 18 months the participation rate was 96.3% among surviving patients.

4.6.2 Study II

The aim was to identify determinants for postoperative delirium and its influence on HRQoL after CABG during 36-month follow-up. The material consisted of the original cohort of CABG patients (n=302).

Diagnosis of delirium was clinical and based on criteria which included acute onset and fluctuating course, inattention, delusions, confusion, and cerebral excitement or altered level of consciousness and having a comparatively short duration (Inouye et al. 1993). A definitive criterion was also that temporary medication, i.e. diazepam or haloperidol, was needed to sedate the delirious patient. A case of delirium developing at any time during the primary hospitalization was included in the analysis. Structured neurocognitive tests were not used. Two patients were lost during the operation day and they were excluded. Thus a total of 300 patients remained for final analysis.

Complete data on HRQoL in 36-month follow-up were retrieved for 92.3% of survivors.

4.6.3 Study III

In this study we aimed at determining the value of EuroSCORE in predicting HRQoL for 36 months after CABG.

The study cohort consisted of 302 patients who underwent CABG. Patient-related factors, preoperative clinical state and cardiac-related factors were estimated according to the EuroSCORE criteria (Nashef et al. 1999). Both additive and logistic risk of mortality was calculated for each patient. In the low risk group (score 0–2)

there were 122 patients, in the medium risk group (score 3–5) 128 patients and in the high-risk group (score ≥ 6) 52 patients.

Complete data on the 15D score was available from 263 (87.1%) of patients corresponding 92.3% of survivors.

4.6.4 Study IV

In Study IV patients with chronic stable CAD were included in the analysis. Thus a total of 240 CABG patients and 224 PCI patients were analyzed. The study was not randomized, but it represents fairly realistic material. The primary outcome measure was determination of post-procedural HRQoL using the 15D. Secondary outcomes included all-cause mortality and performance status after 36-month follow-up. Physical performance was defined according to the New York Heart Association (NYHA) classification and recorded both preoperatively and at the follow-up visit after 36 months. Complete 15D data were received on 93.4% of surviving CABG patients and on 94.9% of surviving PCI patients.

4.6.5 Study V

The study was a retrospective sub-analysis of the initial patient cohort of CABG (n=302) and PCI (n=360) patients. The aim was to analyze the frequency of repeated interventions after primary CABG or PCI during a follow-up of 36 months. The option for invasive treatment was not randomized but based on findings in coronary angiography and on clinical decision-making. Lesions with stenosis of more than 50% of the luminal diameter in a coronary artery were considered significant on the diagnostic angiogram. The cardiologist usually opted for PCI with the patient's concurrence whereas cardiologists and cardiac surgeons always discussed the decision for CABG.

PCI was performed on 360 patients in order to dilate the culprit lesion(s) of the coronary arteries. 302 patients were referred to CABG for optimal coronary revascularization. Coronary stenting used a stent available on perception of lesion requirements. The median of coronary artery lesions treated by PCI was 1 (range 1–3). Coronary stenting was performed in 91.4% of procedures. In the CABG group 283 (93.7%) patients were operated on by the standard cardiopulmonary bypass technique, using continuous retrograde blood cardioplegia, whereas 19 (6.3%) operations were minimally invasive direct (MIDCAB) or off-pump (OPCAB)

operations. A median of 4 (range 1–7) anastomoses was performed. The internal thoracic artery (ITA) was used in 93.4% of operations.

5 RESULTS

5.1 HRQoL for 18 months after coronary artery bypass grafting

The mean 15D score of CABG patients at baseline and that of the age- and gender-standardized reference sample (n=4111) were compared. The baseline scores were 0.8293 (SD 0.0921) and 0.8709 (SD 0.0890) respectively, ($p < 0.001$) (Figure 8). The patients fared significantly worse on eight dimensions out of fifteen, e.g. mobility, vision, breathing, sleeping, usual activities, distress, vitality and sexual activity. By contrast the score for mental function was higher in the patient cohort than in the reference material.

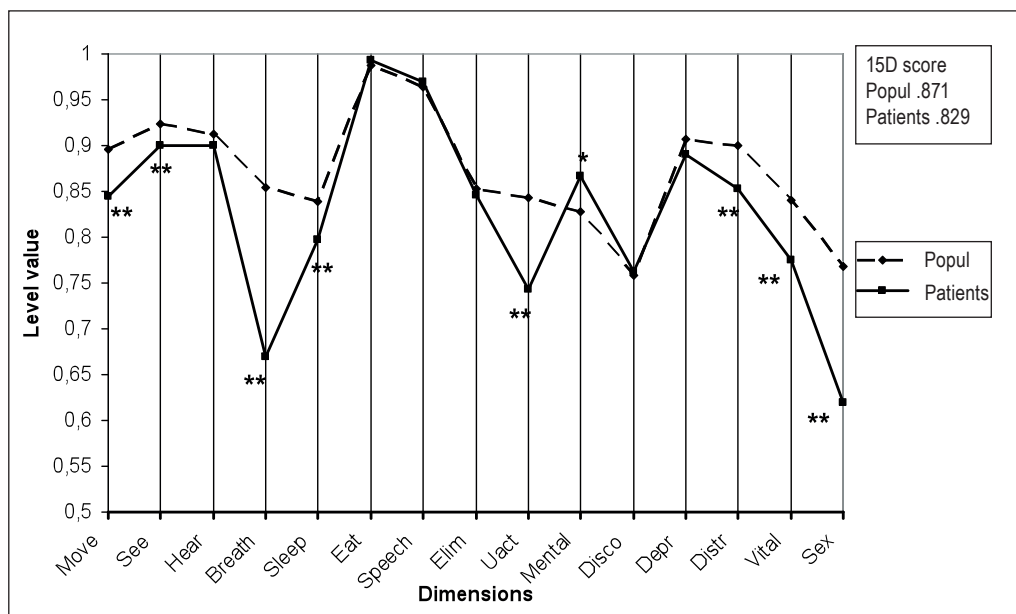


FIGURE 8. Baseline (preoperative) 15D profiles of CABG patients in comparison to the reference population of Health 2000 project of the National Public Health Institute. * $p < 0.01$, ** $p < 0.001$.

The mean 15D score of the CABG patients improved significantly during the first six months after surgery. A downturn followed from 6 months onwards until 18 months, but the mean 15D score of the surviving patients remained still at a higher level than before surgery ($p < 0.001$).

Male patients had a higher 15D score at baseline than females ($p = 0.006$). Males also retained a higher score than female patients at 6 months and at 18 months, but the difference was no longer statistically significant ($p = 0.185$ and 0.165 respectively). Moreover, the youngest age group evidenced an appreciable advance in the 15D score at each measurement point in comparison to older age groups: significance for difference was < 0.001 before operation, 0.003 at six months, and < 0.001 at 18 months.

In both genders the index score improved at the beginning of recovery in the same manner, but from six months onwards the index score declined again for both male and female patients. However, the score remained at a significantly higher level for both genders than at baseline (Figure 9).

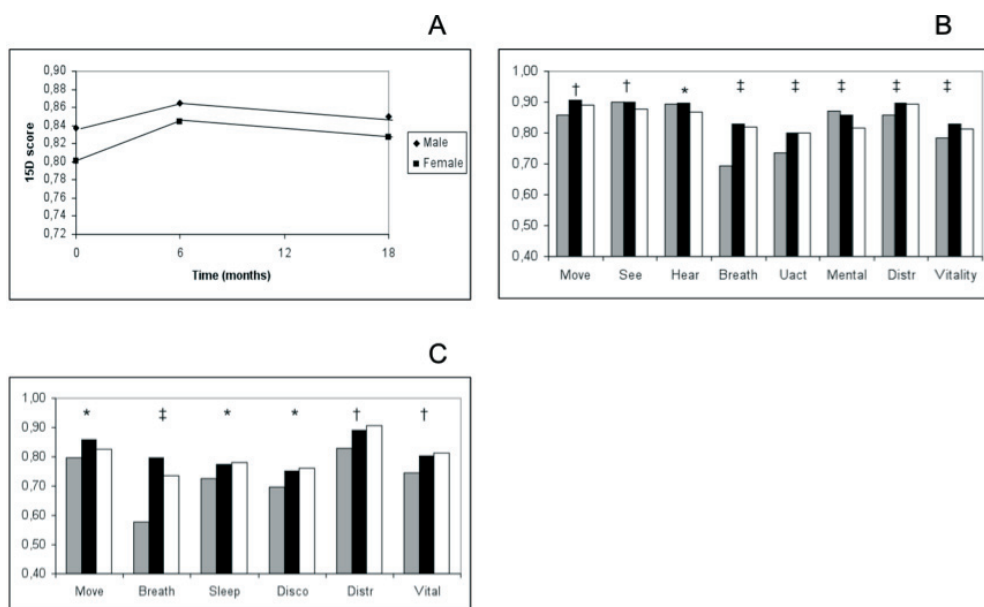


FIGURE 9. Changes in the mean 15D index score up to 18 months by gender (A). The mean level values of the 15D dimensions with statistically significant change ($* p < 0.05$, $† p < 0.01$, $‡ p < 0.001$) are shown separately for male (B) and female (C) patients. Preoperative state in grey, 6 months in black and 18 months in white columns.

In each of the three age groups, i.e. patients <65 yrs, 65–74 yrs and >75 yrs, the 15D score improved considerably during the first 6 months followed by a downturn from 6 months onwards to 18 months (Figure 10). In surviving patients older than 75 years the subsequent decline was steeper than in the younger ages, and the mean 15D score of this age group returned to the preoperative level and even to a slightly lower level than before surgery.

During the first six months postoperatively there were seven dimensions on which the patient sample experienced a significant improvement: mobility, breathing, usual activities, discomfort and symptoms, distress, vitality and sexual activity. Only on one dimension, the mental function, there was seen downward trend ($p=0.057$). In male patients a significant improvement was seen on the dimensions of mobility, breathing, usual activities, distress and vitality, whereas female patients experienced a positive change in mobility, breathing, sleeping, discomforts and symptoms, distress and vitality (Figure 10[B] and 10[C]). Changes in the dimension level values became fewer and smaller with increasing age, and in the age group >75 years only hearing and breathing improved significantly during the first six months postoperatively (Figure 9[D]).

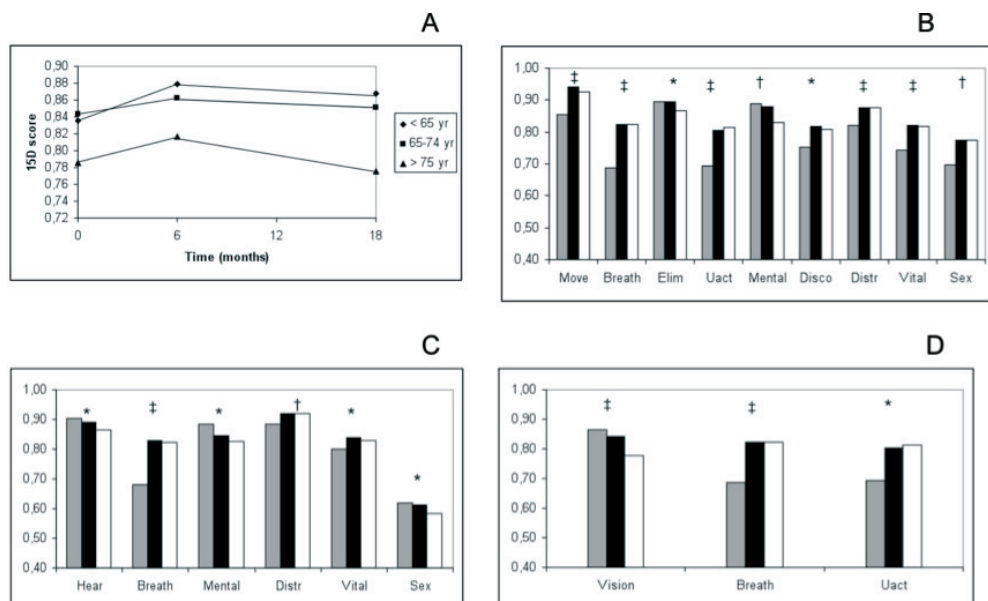


FIGURE 10. Trends in the mean 15D score in different age groups (A). The mean level values of the 15D dimensions are shown for patients <65 yrs (B), 65–74 yrs (C) and >75 yrs (D). Only dimensions of significant change (* $p<0.05$, † $p<0.01$, ‡ $p<0.001$) are given. Grey columns depict preoperative state, black columns at 6 months and white columns at 18 months after CABG.

Between 6 and 18 months in follow-up, a significant decline for the total cohort was seen on seven dimensions, i.e. mobility, vision, hearing, elimination, usual activities, mental function and sexual activity and on three dimensions (hearing, elimination, mental function) the mean score value was even lower at 18 months than before the operation (Figure 11).

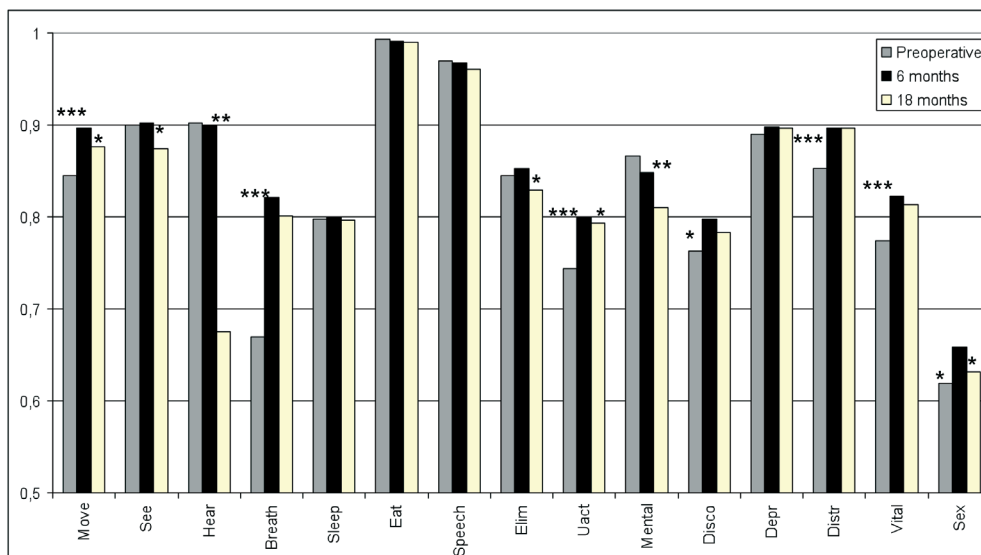


FIGURE 11. The mean level values of the 15D dimensions of CABG patients during the observation time. P-values are given only in case of significant difference (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$).

5.2 Postoperative delirium and HRQoL after CABG

The incidence of delirium was 6.0 % during the primary hospitalization after CABG. All these patients had undergone conventional CABG with CPB. In comparison to the patients without postoperative delirium the patients with delirium were older and more often had a history of CVD ($p = 0.002$) and higher incidence of CHF. Both additive and logistic EuroSCORE was higher in this group (Table 5). Moreover, five patients out of 18 with postoperative delirium (27.8%) and 15 patients without delirium (5.3%) ($p = 0.001$) had a history of malignancy, all in remission at the time of the operation. One patient in the delirium group and two patients in the no-delirium group had a history of heavy alcohol abuse before the operation.

Postoperatively patients who developed delirium were more frequently subjected to re-sternotomy for bleeding ($p = 0.036$) and they also needed more often vasoactive support for hemodynamic stabilization on the first postoperative morning ($p = 0.017$).

They also experienced more often both readmission to the ICU ($p<0.001$) and reintubation ($p<0.001$). Postoperative complications, such as pneumonia ($p=0.006$) and AF ($p=0.004$) were more common in patients with delirium. Stay in the ICU and total length of hospitalization including recovery in other medical care units was also longer in this patient group. Cumulative survival was 96.1% in patients without delirium and 77.8% in patients with delirium (log-rank test: $p<0.001$) at three years.

TABLE 5. Univariate analysis of preoperative variables of CABG patients with or without postoperative delirium.

Variable	No delirium n = 282 %	Delirium n = 18 %	P-value
Age, years (SD)[range]	65.8 (9.0) [44.1–84.5]	72.0 (7.0) [54.2– 80.1]	0.005
Male gender	78.1	94.4	0.136
Chronic pulmonary disease	9.6	16.7	0.405
Extracardiac arteriopathy	4.6	5.6	0.588
Neurological dysfunction	0.4	0	1.000
Previous cardiac surgery	3.2	0	1.000
Renal dysfunction	0	5.6	0.060
Unstable angina	9.9	16.7	0.413
LVEF 30 – 49 %	42.9	50.0	0.627
LVEF < 30 %	3.2	5.6	0.467
Recent myocardial infarction	9.9	16.7	0.413
Pulmonary hypertension	0.4	5.6	0.117
Emergency	1.1	5.6	0.220
Diabetes	26.6	11.1	0.174
Hypercholesterolemia	70.9	72.2	1.000
Hypertension	55.7	66.7	0.465
Previous cerebral disease	6.7	33.3	0.002
Chronic heart failure	2.8	16.7	0.022
NYHA Class 3 - 4	61.3	66.7	0.653
ASA 4	42.9	50.0	0.556
EuroSCORE, additive, mean (SD)	3.3 (2.3)	4.9 (2.5)	0.007
EuroSCORE, logistic, mean (SD)	3.3 (3.8)	5.3 (4.5)	0.005

When adjusted for age, gender, CVD, CHF, chronic renal insufficiency and additive EuroSCORE, age cerebral disease, CHF and male gender had an independent

influence on postoperative delirium. On the other hand, among postoperative complications, pneumonia and LOS were predictors for delirium. The result of logistic multivariate analysis is summarized in Table 6.

Preoperative 15D score differed between patients with delirium and patients without delirium (0.774 vs. 0.833, $p=0.024$). Patients with postoperative delirium had poorer preoperative score on five out of fifteen dimensions: seeing, hearing, eating, speaking and elimination (Figure 12).

TABLE 6. Logistic multivariate analysis for predictors of delirium after CABG.

Variable	Odds ratio	95% CI	P-value
Age	1.08	1.01–1.17	0.029
CVD	4.91	1.43–16.85	0.011
CHF	5.28	1.02–27.29	0.047
Male gender	7.60	0.93–62.20	0.059
Postoperative pneumonia	5.34	1.64–17.37	0.005
LOS	4.71	1.29–17.13	0.019

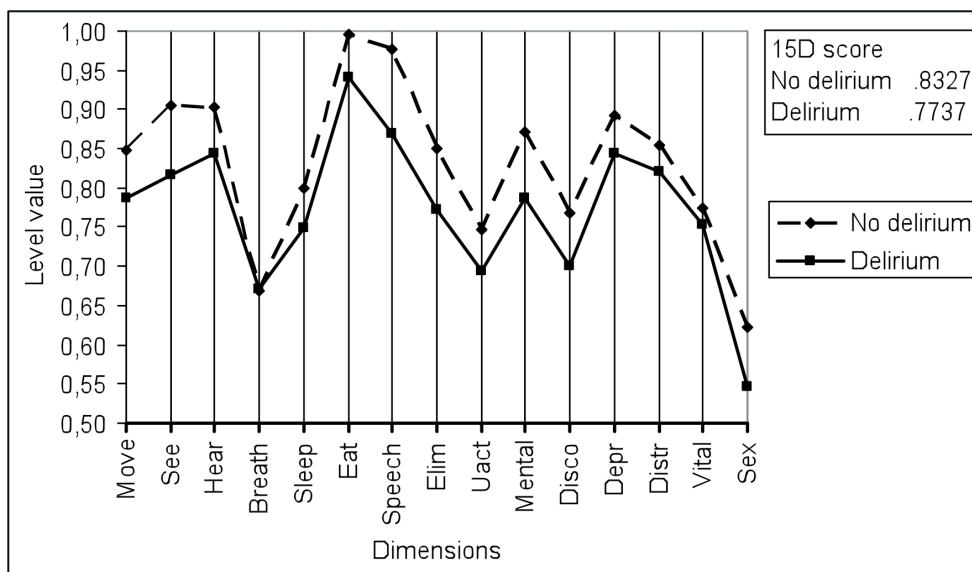


FIGURE 12. Preoperative 15D profiles and 15D scores of CABG patients with or without delirium.

In the follow-up the mean 15D score of the patients without delirium improved from the preoperative level until six months and also at 18 months after CABG the 15D score of the group was significantly higher than preoperatively. By contrast, in the patients with postoperative delirium the mean 15D score did not change at all during the study period compared to baseline (Figure 13). Moreover, the score tended to deteriorate in patients with high preoperative 15D score (higher than the median for the study cohort) and with postoperative delirium ($n = 5$) during the first 6-month period but improved considerably later on. In patients with low initial score (lower than the median of the cohort) and with postoperative delirium no significant change of score was observed in follow-up (Table 7).

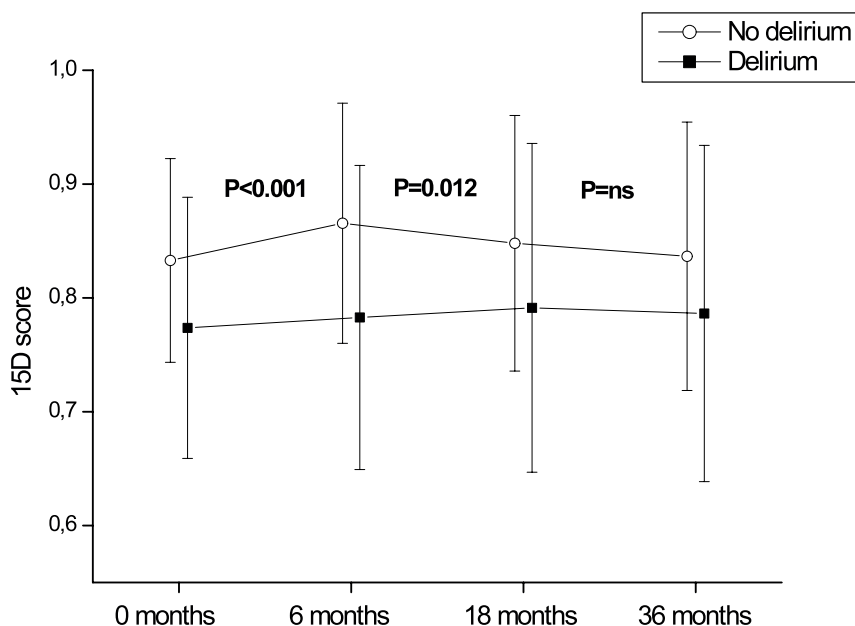


FIGURE 13. The mean 15D index score (\pm SD) of patients without and with delirium during the study period. P-values indicate difference in the 15D score against preoperative level at the time of control.

TABLE 7. 15D score change during 6 months after CABG in patient groups with or without delirium against to median preoperative 15D score (0.8374) of the study cohort.

Patient group	N	Age (mean)	15D score		P-value
			Preoperative	6 months	
Delirium, score >median	5	70.8	0.9225	0.8071	0.080
Delirium, score <median	13	72.4	0.7164	0.7727	0.222
No delirium, score < median	132	66.7	0.7608	0.8187	<0.001

5.3 EuroSCORE predicts HRQoL after CABG

Clinical variables of the three risk groups of CABG patients (n=302) according to the EuroSCORE are reported in Table 8 and postoperative outcome in Table 9. 30-day mortality was 1.0% (1 patient in the low risk group and 2 patients in the high risk group). The length of stay in the ICU was mean 1.04 days (SD 0.20, range 1–2 d), 1.45 days (SD 2.36, range 1–23 d), and 4.52 days (SD 20.64, range 1-150), in the low, medium and high-risk groups respectively (p=0.001). Postoperative stroke, neuropsychological complications (i.e. confusion or delirium), renal failure and AF occurred significantly more often in the high-risk patient group.

TABLE 8. Distribution of risk factors in patients undergoing CABG according to different operative risk as assessed by EuroSCORE.

Preoperative variables ^a	Additive EuroSCORE			P-value
	0–2	3–5	6–14	
Proportion of patients	40.4	42.4	17.2	
Mean age, years (SD)	59.2 (6.7)	69.2 (6.7)	75.6 (5.4)	< 0.001
Female gender	9.0	26.5	34.6	< 0.001
Pulmonary disease	4.9	11.7	17.3	0.030
Extracardiac arteriopathy	1.7	3.9	13.5	0.003
Neurological dysfunction	0	0	1.9	0.172
Previous cardiac surgery	0	3.1	11.5	0.001
Renal failure	0	0	1.9	0.172
Unstable angina	1.7	11.7	28.8	< 0.001
LVEF 30 - 49%	31.1	48.4	59.6	0.001
LVEF < 30 %	0	3.1	11.5	0.001
Recent MI	0.8	8.6	38.5	< 0.001
Pulmonary hypertension	0	0.8	1.9	0.315
Emergency	0	0	7.7	0.001
NYHA 3-4	49.2	65.6	82.4	< 0.001

^a Values as percentages

The 3-year survival was 96.7%, 95.3% and 86.5% in the low, medium and high risk groups respectively ($p=0.025$).

Complete data on the 15D score was available from 263 (87.1%) of patients (92.3% of survivors). In these patients additive EuroSCORE correlated significantly with the preoperative ($\rho: -0.185$, $p=0.003$), 6-month ($\rho: -0.170$, $p=0.006$), 18-month ($\rho: -0.224$, $p<0.0001$) and 36-month ($\rho: -0.271$, $p<0.0001$) 15D scores. Similarly logistic EuroSCORE also correlated significantly with the preoperative ($\rho: -0.200$, $p=0.001$), 6-month ($\rho: -0.180$, $p=0.003$), 18-month ($\rho: -0.223$, $P < 0.0001$) and 36-month ($\rho: -0.275$, $p<0.0001$) 15D scores. The correlation increased along with the duration of follow-up.

TABLE 9. Postoperative outcome according to different operative risk as assessed by EuroSCORE.

Outcome end-points ^a	Additive EuroSCORE			P-value
	0–2	3–5	6–14	
30-day mortality	0.8	0	3.8	< 0.001
Prolonged ICU stay ^b	0	5.4	15.4	< 0.001
Readmission to ICU	0.8	3.1	5.8	0.118
Total postoperative hospital stay (days), mean \pm SD (range) ^c	9.6 \pm 4.6 (3–16)	11.9 \pm 6.5 (5–56)	15.9 \pm 24.4 (0–179)	< 0.001
Reoperation for bleeding	4.9	4.7	1.9	0.818
Perioperative MI	7.4	14.1	11.5	0.235
Sepsis	0	3.1	1.9	0.152
Pneumonia	6.6	7.0	9.6	0.769
Deep sternal wound infection	0.8	0.8	1.9	0.574
Stroke	0	3.9	5.8	0.048
Delirium or confusion	2.5	5.5	15.4	0.004
Renal failure	0	4.7	3.8	0.030
Atrial fibrillation	36.1	44.5	63.5	0.004

^a Values as percentages; ^b Primary ICU stay + possible readmission stay on ICU; ^c Includes also the length of stay in other units of medical care after discharge from the operating hospital.

The 15D score improved until 6 months (289 survivors, $p<0.0001$) and despite a decline from 6 months onwards the score was still significantly higher at 18 months than preoperatively (282 survivors, $p=0.001$) (Figure 14). Interestingly, the impairment continued from 18 months onwards and at 36 months after the operation the 15D score approached the preoperative level.

Clinical improvement (change in 15D score >0.03) was seen in 50.6% of patients at 6 months, 40.0% at 18 months and 35.9% at 36 months.

At all study intervals a significant difference was observed in the 15D scores between the groups of increasing additive EuroSCORE. This finding was confirmed by the repeated-measures test ($p=0.001$) (Figure 15). However, the rate of clinically significant increase in the 15D score was similar among the risk groups at 6 and 18 months, but tended to decrease towards 36 months in the medium and the high-risk group. Thus, clinical improvement was evident in 46.8% of low risk patients, in 34.8% of medium risk patients and in 33.3% of high-risk patients ($p=0.13$) at 36 months.

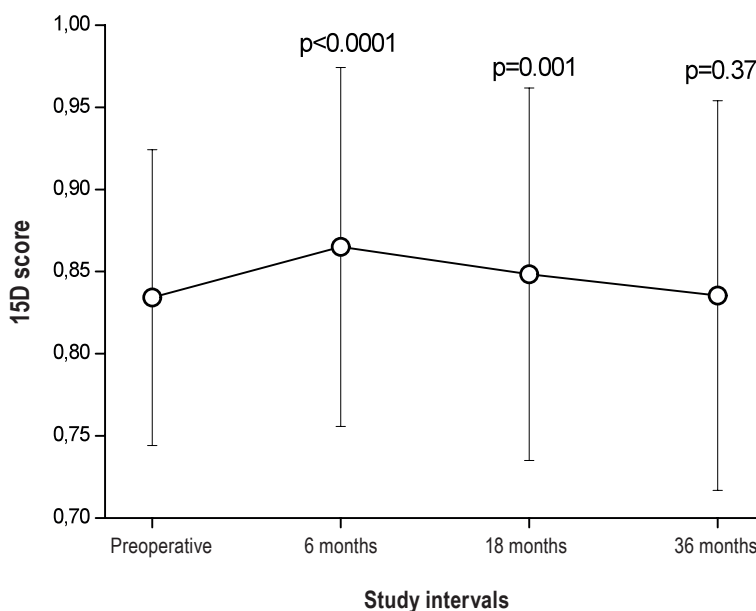


FIGURE 14. Graph showing changes (\pm SD) in the 15D score during the study intervals compared to preoperative score among 36-month survivors with complete data (263 patients). P-values are according to the Wilcoxon test.

The ROC curve analysis showed that neither the additive EuroSCORE (area under the curve [AUC]: 0.490, $p=0.78$ and AUC: 0.534, $p=0.34$ respectively) nor the logistic EuroSCORE (AUC: 0.491, $p=0.81$ and AUC: 0.526, $p=0.47$ respectively) were predictors of clinically important increase of the 15D score at 6 and 18 months. Both additive (AUC: 0.582, $p=0.024$) and logistic EuroSCORE (AUC: 0.575, $p=0.039$) were predictors of a clinically important increase of 15D score at 36 months. However, the AUCs were far from being optimal.

The best cut-off value of the additive EuroSCORE for the prediction of a clinically significant improvement of the 15D score was 3 at 36-month follow-up. Among patients with a EuroSCORE from 0 to 3, the rate of clinically significant

improvement of the 15D score was 46.7%, whereas it was 30.1% among those with an additive EuroSCORE >3 (p=0.006, sensitivity 67.3%, specificity 50.3%, accuracy 57.0%). This cut-off did not predict clinically significant improvement of the 15D score at either 6 months (p=0.83) or 18 months (p=0.52). Figure 15 shows the pattern of change in the 15D scores in patients with additive EuroSCORE from 0 to 3 and those with an additive EuroSCORE from 4 to 14.

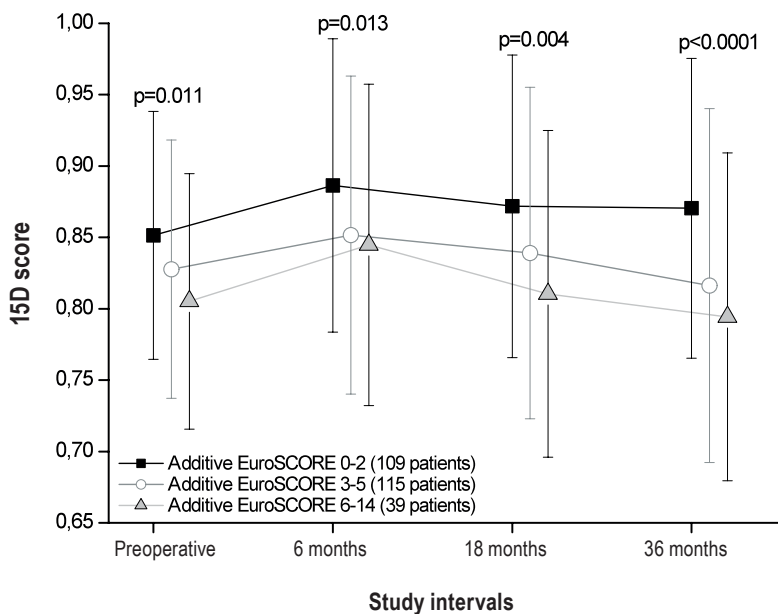


FIGURE 15. Graph showing changes (\pm SD) in the 15D score during the study intervals among 36-month survivors with complete data (263 patients). P-values are according to the Kruskal-Wallis test. The differences between the study groups were also significant according to the repeated measure test (p=0.001).

5.4 HRQoL after CABG or PCI in the management of chronic stable CAD

Baseline characteristics of patients with chronic stable CAD are presented in Table 10. The median follow-up was 36.0 months for the patients of the study cohort. The mean age as well as the patients' age distribution was equal between CABG and PCI patients. The proportion of female patients was significantly higher in the PCI group (p=0.004). Both the structural (i.e. coronary artery lesions) as well as the functional status of the heart (i.e. LVEF) was poorer in CABG patients. The same concerns preoperative state of performance (NYHA class). Medians of 4 (range 1-4)

anastomoses were performed surgically. The median number of coronary artery lesions treated by PCI was 1 (range 1–3). Coronary stenting with an available stent was performed in 87% of procedures.

Thirty-day mortality was 0.8% (2 patients) in the CABG group and 0% in the PCI group. Three-year survival was 95.0% and 95.6%, correspondingly ($p=0.677$).

TABLE 10. Baseline characteristics of patients with chronic stable CAD.

Characteristics	CABG n =240 %	PCI n = 229 %	P-value
Age, years (SD)	66.1 (8.8)	64.5 (10.2)	0.064
Sex			
Female	20.6	31.4	0.004
Age groups			0.164
< 65 yr	39.2	47.6	
6–74 yr	44.2	36.7	
> 75 yr	16.7	15.8	
LVEF			<0.001
< 30%	2.9	1.3	
30–50%	42.1	17.9	
> 50%	54.5	59.8	
Previous MI	33.3	24.5	0.042
Hypertension	54.6	57.6	0.516
Hyperlipidaemia	73.3	69.4	0.359
Diabetes	25.8	18.3	0.059
COPD	10.0	10.0	1.000
ASO	10.8	8.3	0.433
Previous PCI	5.0	7.9	0.258
Previous CABG	3.3	8.3	0.028
NYHA Class			<0.001
Class I	2.1	11.4	
Class II	44.2	45.0	
Class III	47.9	39.7	
Class IV	5.8	3.9	
Data missing	0.4	21.3	
LMCA stenosis > 50 %	29.6	2.2	<0.001
No. of diseased vessels			<0.001
3-VD	65.0	14.8	
2-VD	28.8	34.9	
1-VD	6.3	50.2	

LVEF, left ventricular ejection fraction; MI, myocardial infarction; COPD, chronic obstructive pulmonary disease; ASO, arteriosclerosis obliterans (peripheral or carotid artery disease); NYHA, New York Heart Association; LMCA, left main coronary artery; VD, vessel disease.

The mean 15D score reflecting preoperative quality of life, was 0.8275 (SD 0.0891) for CABG patients and 0.8321 (SD 0.0986) for PCI patients (NS). In the follow-up the mean 15D score improved significantly from the preoperative level until six months in both groups (0.8579, SD 0.1095, $p < 0.001$ for CABG and 0.8456, SD 0.1054, $p = 0.009$ for PCI group). Thus, the change was statistically significant in both groups and clinically relevant for the CABG patients. The mean 15D score deteriorated during the later observation period and returned to the same level as before the intervention in both groups by 36 months (Figure 16). Changes in the 15D score occurred as a function of time, but when the mean 15D score was compared between the study groups of CABG and PCI patients at different observation times no statistical difference was found. This finding was also independent of age.

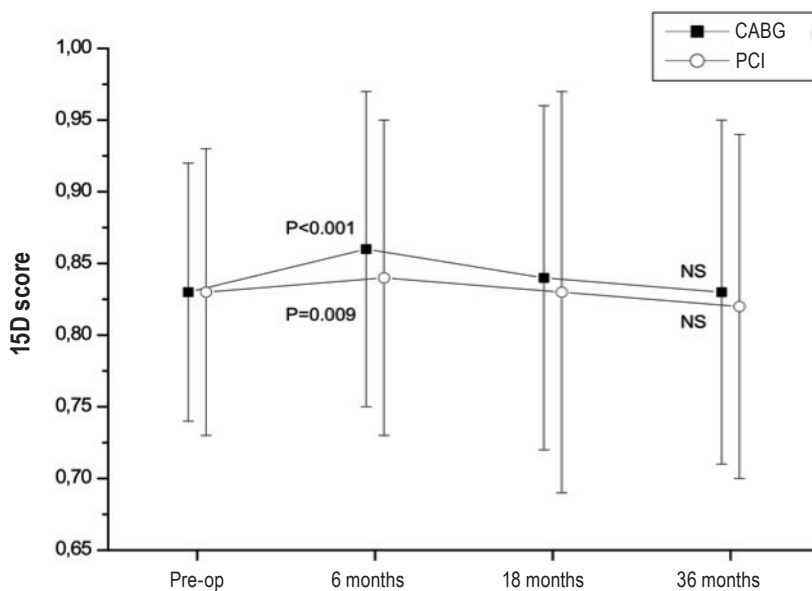


FIGURE 16. 15D level score of the study groups. Statistical difference is reported against preoperative level separately for CABG and PCI patients.

During the first six months after the intervention improvement was seen on six dimensions (moving, breathing, usual activities, discomfort and symptoms, distress, and vitality) among the CABG patients and on five dimensions (breathing, usual activities, discomfort and symptoms, depression, vitality) among the PCI patients.

At up to 36 months a significant improvement was still seen in breathing, in distress and symptoms and in vitality among the CABG patients and in breathing among the PCI patients. Five dimensions of the 15D (mobility, breathing, usual activities, discomfort and symptoms and vitality) describe the physical experiences of humans and may be important in estimating development of HRQoL after invasive treatment for CAD patients. In CABG patients all mentioned dimensions improved during the first six months after the intervention, whereas PCI patients improved on four of these dimensions. Clinically relevant improvement was more frequent in the CABG group than in the PCI group between 0- 6 months (48.9% vs. 36.6%, $p=0.008$) as well as between 0–36 months (39.8% vs. 27.6%, $p=0.010$). However, 21.6% of CABG patients and 25.0% of PCI patients experienced clinically relevant decline between 0–6 months ($p=0.438$). Between preoperative time and at 36 months the frequencies were 36.1% and 32.9% ($p=0.541$) respectively (Table 11). However, the 15D score of the reference population was higher than that of the study cohort 36 months after the treatment ($p<0.001$) (Figure 17).

TABLE 11. Clinically noticeable change of HRQoL among the study groups.

	CABG		PCI		P-value
	# of patients	%	# of patients	%	
<i>Clinical improvement</i>					
0–6 months	113/231	48.9	82/224	36.6	0.008
0–36 months	86/216	39.8	58/210	27.6	0.010
<i>Clinical impairment</i>					
0–6 months	50/231	21.6	56/224	25.0	0.438
0–36 months	78/216	36.1	69/210	32.9	0.541

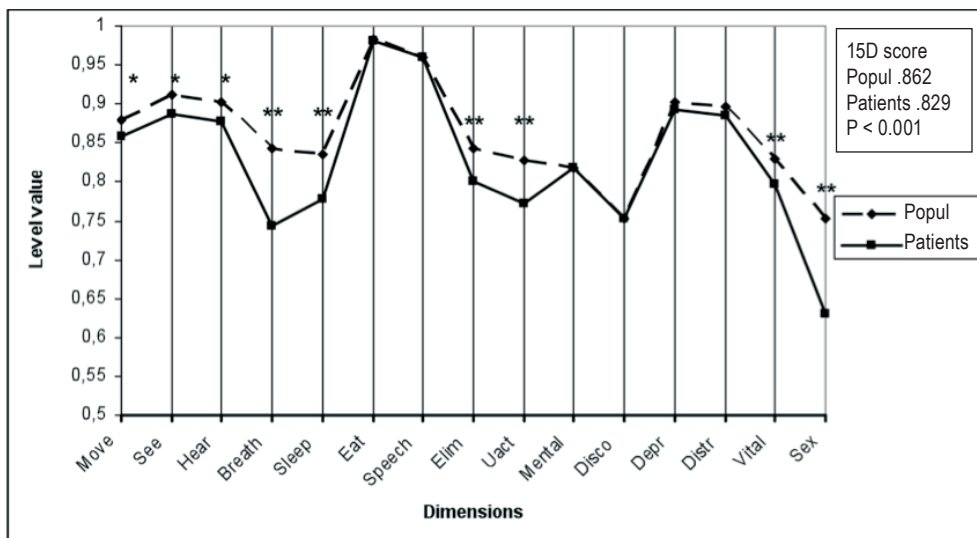


FIGURE 17. 15D profiles and scores of the study cohort of CABG and PCI patients 36 months after treatment in comparison to the reference population. * $p < 0.05$, ** $p < 0.001$.

A total of 85.9% of CABG patients and 67.5% of PCI patients improved the performance state and their NYHA Class was at least one step lower after three years of the treatment than before it. The difference was significant in favor of the CABG group ($p < 0.001$). Moreover, 68.3% of CABG patients and 58.3% of PCI patients reported that they were asymptomatic in their normal lives after 3 years ($p = 0.022$). Postoperative NYHA was significantly better in the CABG group (Mann-Whitney U-test $p = 0.025$). Patients in the PCI group also underwent both repeat PCI (14.8% vs. 1.3%, $p < 0.001$) and repeat CABG (5.7% vs. 0.8%, $p = 0.003$) significantly more frequently than CABG patients within the following 3 years after the initial intervention.

5.5 Repeat intervention after invasive treatment of coronary arteries

A total of 662 CAD patients were reviewed retrospectively. The intervention performed was not random but based on clinical decision-making in this so-called real-world material. 302 patients initially underwent CABG and 360 patients PCI. The mean age of the patients undergoing PCI was lower and there were more females in that group (29.4% vs. 20.9%, $p = 0.007$). Diabetic patients underwent CABG more often than PCI ($p = 0.023$). Univariate analysis on the basic variables of the groups is presented in Table 3. Considering the state of physical performance, PCI patients

were more frequently initially in NYHA class 1 and in class 4. Patients undergoing surgery had 3-VD and significant LM stenosis more often but also a poorer EF of the heart. 17.2% of CABG patients were at high risk of mortality according to EuroSCORE. No comparable risk analysis was available for PCI patients.

Cumulative all-cause mortality was equal in the groups and 3-year survival was 95.6% for the PCI group and 94.4% for the CABG group ($p=0.094$).

A total of 147 PCI patients underwent repeat angiography and, moreover, 45 patients were re-examined 2–4 times during the 3-year follow-up (Table 12). The cumulative number of repeat angiographies was 207 and the cumulative frequency 57.7% in the PCI group.

Indication for the first repeat examination was recurrent angina or recent MI in 74.1% of cases and a control or a planned sequential procedure after the primary treatment in 25.9% of cases. Recurrent angina or MI indicated cumulatively 73.5% and control of the status of treated coronary lesion(s) 26.5% of repeat examinations. By contrast, 13 patients (4.3%) in the CABG group needed a new angiography during follow-up. The frequency was significantly lower than for PCI patients ($p<0.001$). A total of three CABG patients (1.0%) were re-examined by angiography on the first postoperative day due to significant elevation of myocardial enzymes immediately after surgery. Later on recurrent angina or a recent MI indicated 90.0% of new angiographies for CABG patients and 10.0% were performed to check the state of bypass grafts.

TABLE 12. Repeat coronary angiography or invasive treatment (PCI, CABG) after coronary artery intervention during 36-month follow-up. Values of variables are presented as number of patients.

Procedure	CABG (n = 302)	PCI (n = 360)	P-value
Angiography			
Once	13	147	<0.001
Twice	0	45	
Three times	0	12	
Four times	0	3	
PCI			
Once	3	60	<0.001
Twice	0	12	
CABG			
Once	2	24	<0.001
Twice	0	1	

In addition to repeat angiographies patients in both groups underwent repeat invasive treatments due to new symptoms and angiography findings. Thus, a

new PCI was performed for 17.3% of PCI patients and for 3.2% of CABG patients ($p < 0.001$) during the 3-year follow-up. Moreover, 12 PCI patients (3.5%) underwent a repeat PCI twice by the end of follow-up (Figure 18). Frequency of repeat CABG was 6.7% (24 patients) in the PCI group and 0.7% (2 patients) in the CABG group ($p < 0.001$) (Figure 19). In Cox regression analysis HR for repeat PCI after initial PCI was 8.5 (95 % CI 3.7–19.5, $p < 0.001$) and for repeat CABG 9.5 (95% CI 2.2–40.0, $p = 0.002$) in comparison to initial CABG. The main findings and reasons for repeated interventions are presented in Table 13.

TABLE 13. Indications and findings of repeated angiographies for the PCI and CABG patients.

	# of patients	New symptom		Recent MI		Control for previous treatment		Restenosis		Progression of CAD	
		n	%	n	%	n	%	n	%	n	%
<i>PCI patients</i>											
1 st repeat	147	109	74	16	10	38	26	43	29	37	25
2 nd repeat	45	35	78	8	18	10	22	8	18	14	31
3 rd repeat	12	6	50	0	0	6	50	2	17	3	25
4 th repeat	3	3	100	1	33	0	0	0	0	1	33
<i>CABG patients</i>											
1 st repeat	13	12	92	5	39	1	8			7	54
2 nd repeat	3	3	100	0	0	0	0			2	67

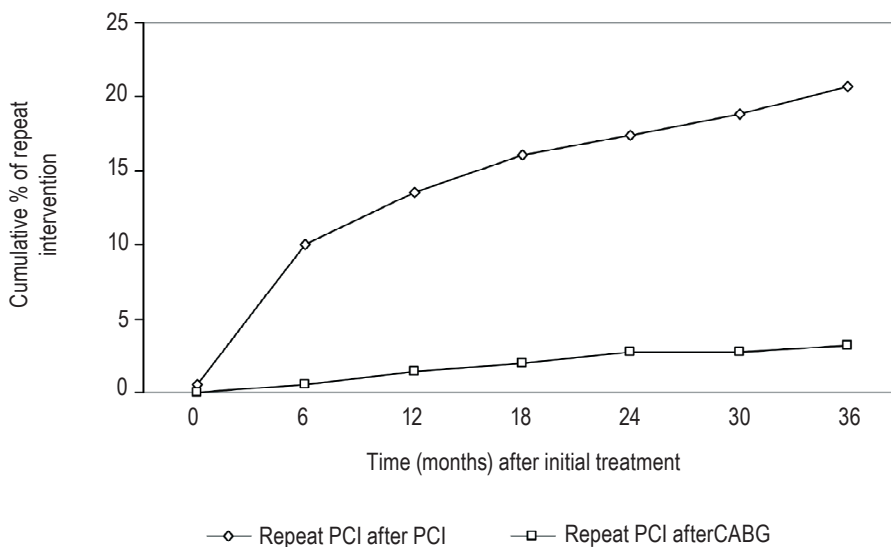


FIGURE 18. Cumulative percentage of repeat percutaneous interventions for PCI and CABG patients within 36 months.

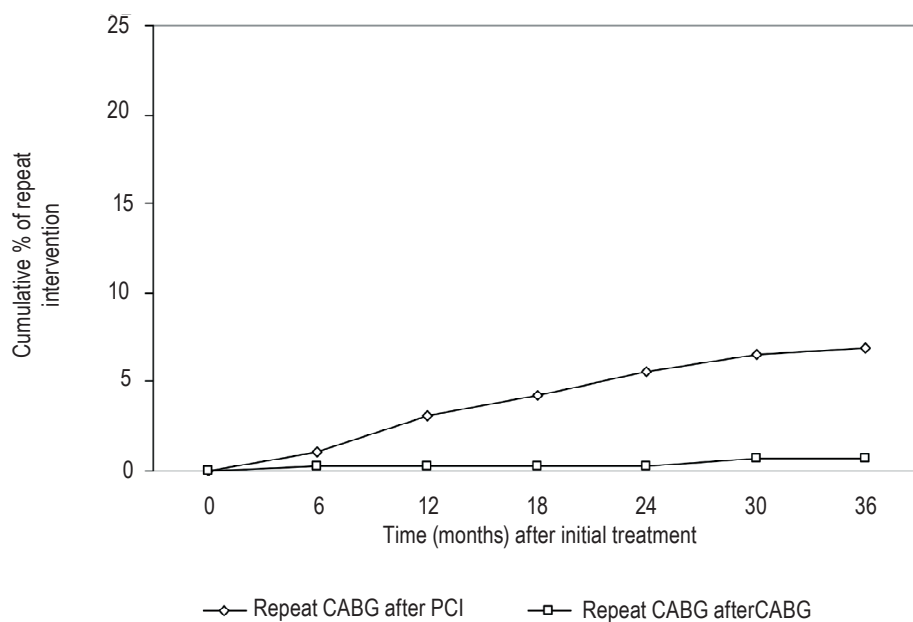


FIGURE 19. Cumulative percentage of repeat CABG for patients undergoing CABG after initial PCI or CABG in the follow-up of 36 months.

6 DISCUSSION

6.1 General considerations

Outcome after invasive treatment for CAD is traditionally assessed in terms of major adverse events i.e. in-hospital mortality, cardiovascular complications and long-term survival (Caine et al. 1991). These ‘hard endpoints’ form the basis on follow-up studies and registries and enable comparisons between treatment modalities in randomized trials. Strict categorising of the used endpoints is naturally essential.

However, outcome cannot be assessed solely in objective terms, as such indicators do not explain how people perceive and experience their lives. The emphasis has been subsequently on also assessing outcome in terms of patients’ perception of changes in their state of health over time and how this affects their lives. Patient reported health status has become increasingly important as a predictor of early morbid outcomes after CABG (Gill et al. 1994, Duits et al. 1997, Rumsfeld et al. 1999, Kind 2001, Curtis et al. 2002, Koch et al. 2007). Patients are interested in their quality of life following an intervention and they may appreciate this endpoint actually more than clinicians do. This has led clinicians and researchers to quantify the impact of specific interventions (Spertus et al. 2002). Patient-centred outcomes are of value both for risk assessment and as an outcome measure (Koch et al. 2008). Moreover, the ACC/AHA guidelines for CABG surgery suggest that improvement in quality of life is a primary indication for this treatment option. (Eagle et al. 1999 and 2004). On the other side, responsiveness of generic measures to detect clinical changes in the course of patients’ CAD has been questioned (Spertus et al. 1994).

Understanding quality of life has today become more important in health care, which – as a system – provides care assuming it promotes general health and alleviates illness and its effects on an individual’s life. It has become fashionable to describe health outcomes in terms of their impact on QoL. In addition to forming

an important endpoint in many diseases, invasively treated CAD included, QoL achieved also has consequences in health care economics. Decisions on what treatments to invest most in are closely related to their effect on patients' quality of life. Finally, combining QoL as outcome and economic resources used to accomplish the state, we can make an objective attempt to compare the effect and impressiveness of various modalities of health care in forms of quality-adjusted life years (QALY).

6.2 The rationale of the present study

The rationale of the present study was to define how patients who had undergone invasive treatment in a little unit providing cardiac intervention experienced their life in long-term follow-up. The topic was extraordinarily interesting because of the decidedly high mean age of the patient population in our clinic. On the other hand the patient material was gathered from a relatively distinctly determined area in Western Finland. From this point of view the rationale was population based. Moreover, the literature gives several examples of studies on HRQoL outcome of diseases in which the treatment given is supposed to change significantly an individual's QoL. Thus, the subject of this research is relevant from both clinically and scientifically.

6.3 HRQoL after CABG in the light of the present study

The general opinion is that HRQoL improves after CABG surgery. One reaches this perception easily when interviewing individuals who have undergone cardiac operation some months or some years afterwards. However, merely asking questions is not sufficient. To obtain relevant and scientifically reliable information we have to use specific measures that objectively reflect changes in QoL after treatment. Diseases have an impact on general function, and assuming that all diseases have a general effect on the quality of life generic, non-disease-specific measures have been developed to evaluate HRQoL. The specific scales of QoL measures will also provide additional information relevant to the condition and treatment under scrutiny. Thus, to penetrate HRQoL more deeply, both generic and disease-specific measures may be required (Kaplan 1988, Bech 1993).

CAD compromises HRQoL extensively. In the present study this was reflected in a poorer baseline 15D score among CABG patients (Study I) than in the general population. Before surgery the mean 15D score of CABG patients (0.8293) was

significantly lower than that of the age- and gender-matched reference sample (0.8709, $p < 0.001$). The patients were significantly worse off on eight dimensions out of fifteen, e.g. mobility, vision, breathing, sleeping, usual activities, distress, vitality and sexual activity. On the other hand the score of mental function, characterizing memory, was higher in the study cohort than in the reference population. In the existing literature Lukkarinen (1998) and Kattainen et al. (2005) compared the basic HRQoL of patients with that of general population, matched for age and gender and the finding was parallel in these studies. Usually authors have had no reference material at all, or comparison has been made with coronary artery diseased patients receiving some other therapy for CAD, medical treatment or PCI. We did not compare the pre-interventional HRQoL of PCI patients with the HRQoL scores of the reference population, but as seen in the data of original communications IV and V, the demographic characteristics were quite similar among CABG and PCI patient groups. Thus we can with justification assume that the basic HRQoL of PCI patients was also inferior to that of general population. Interestingly, the difference in the basic mean score was more pronounced in Kattainen and co-authors' study than in the present study, although the age-structure favoured the earlier one.

The measure used for assessing HRQoL, the 15D, is generic and lacks an item that directly reflects the angina pectoris typical of CAD patients. Patients experience angina often as breathlessness or a constricting sensation in the chest. Thus the dimension 'breathing' and its deteriorating in exercise, comes close to the sense of angina. Patients in the present study – as in the study by Kattainen et al. (2005) – had significantly lower scores on the aforementioned dimension when compared to the reference population, reflecting problems with cardiovascular function. Cardiac problems are also expressed in the dimensions 'moving', 'usual activities', 'distress and symptoms' and 'vitality', in which patients scored significantly lower than the reference population. The inferior scores in these domains reduce the total 15D score and reflect poorer HRQoL. Kattainen et al. made a more detailed analysis and concluded using stepwise regression analysis between pre-interventional variables that the more frequently and in lighter activity chest pain occurs, the lower the 15D score. This interpretation seems to be correct although we are not able to confirm it exactly.

The present study demonstrated a significant improvement in the HRQoL of both CABG patients and PCI patients during the first six months after surgery. This finding parallels well that presented in the earlier literature, especially a short time after CABG (Caine et al. 1991, Chocron et al. 1996, Rumsfeld et al. 2004, Kattainen et al. 2005, LeGrande et al. 2006), but also mid-term (Hunt et al. 2000, Falcoz et al. 2003, Järvinen et al. 2003) and long-term (Caine et al. 1999, Herliz et al. a1999, b2003,

c2005, d2008 and Lukkarinen et al. 2006) follow-up and after PTCA (Pocock et al. 2000, Kattainen et al. 2005, Weintraub et al. 2008). Unfortunately our study does not cover the immediate postoperative period of the first week(s), during which domains of physical performance may deteriorate significantly as seen in the study by Elliott and co-authors (Elliott et al. 2006). In the present study a significant improvement took place on dimensions reflecting physical activity and relief from anginal symptoms, i.e. mobility, breathing, usual activities, distress, vitality, discomfort and symptoms and sexual activity. PCI patients achieved a parallel advance, although on a smaller scale. Total improvement was likewise not so pronounced in the PCI group as among CABG patients. Advanced physical functioning in the early recovery phase has been confirmed in several earlier studies (Chocron et al. 1996, Hunt et al. 2000, Rumsfeld et al. 2004, Le Grande et al. 2006, Elliott et al. 2006).

Rapid improvement of HRQoL may be surprising considering the extent of the surgical procedure. CABG patients have a larger number of complications after hospital discharge than PCI patients (Skaggs and Yates 1999). Incision pain and respiratory problems may be the most usual and have been well documented by earlier researchers (Jenkins et al. 1983, Moore 1995). Major complications, such as neurological damage or delayed healing of the chest may lead to poorer HRQoL outcome, but these variables have not been extensively examined (Rumsfeld 2004). Improvement of HRQoL may also reflect fulfilment of expectations for an individual patient after successful course from the operation and recovery without major complications or adverse events.

6.4 Two-slope-shaped progress of postinterventional HRQoL

A considerable improvement at the beginning of recovery was, however, followed by stabilization and some impairment in HRQoL, a finding that has also been reported previously (Sjöland et al. 1997, Yun et al. 1999, Herlitz et al. 2003, Falcoz et al. 2006). In the present study the trend of mean 15D scores – rapid progress until 6 months postoperatively followed by subsequent decline – was seen as a common occurrence in the total study cohort, but also in all subgroups of the study material. Thus it was seen in both genders, in various age groups, in both treatment options (CABG or PCI) and moreover in all three EuroSCORE risks groups (low, medium or high risk of mortality). The mean 15D score indicating HRQoL in the whole study group for CABG was significantly higher at six months (p-value for difference 6 months vs. preoperative level <0.0001) and at 18 months (p=0.001) after surgery but reverted to the baseline level by 36 months (p =0.37) (Study III). In Study IV HRQoL improved

in all three EuroSCORE risk groups by six months after surgery and then declined slowly in the low risk group until 36 months and somewhat faster in the groups of medium or high risk during the same time interval.

The explanation for the impaired mean scores of the 15D may be found in closer analysis of changes in individual domains of the 15D. It appears that impairment was seen from 6 months onwards on the dimensions of hearing, seeing, moving, usual activity, mental function and sexual activity. All of these dimensions have a natural tendency to decline at higher ages. In a patient material with as high a mean age as in the present study, a time interval from 12–30 months may be long enough to reveal changes on the aforementioned dimensions and thereby lower the mean 15D score of the group under scrutiny. Of course, individual differences on several dimensions may be significant. Additionally the dimension ‘mental function’ of the 15D describes the level of subjective experience of memory.

A similar two-slope-shaped process seems also to characterize post-interventional HRQoL of the PCI patients. As a group PCI patients achieve rapid improvement during the first months after the invasive treatment, although the progress may not be as substantial as among CABG patients. The mean 15D score achieved in the group was statistically significant ($p=0.009$) in comparison to the baseline score (Study IV). Several earlier studies have observed an improvement in HRQoL after PTCA or PCI in short-term follow-up (Brorsson et al. 1993, Pocock et al. 1996, Währborg 1999, Brorsson et al. 2001, Borkon et al. 2002, Kattainen et al. 2005, Lukkarinen et al. 2006, Favarato et al. 2007). Thus the finding of improved HRQoL after PCI concurs with other studies. However, comparison of the change has been repeated in earlier reports usually only once during the follow-up. Given the literature we are unable to provide an exact answer on the progress of HRQoL after PCI during a long follow-up, because comparisons between two time points give only a linear interpretation of the change. However, the results of the present study confirm the similarity of change in HRQoL after either PCI or CABG.

6.5 HRQoL is associated with gender

Earlier studies have shown that female patients may have poorer outcome after CABG than males (Abramov et al. 2000). This is also reflected in poorer HRQoL outcome (Vaccarino et al. 2003, Phillips Bute et al. 2003, Lindquist et al. 2003, Koch et al. 2004, Gjejlo et al. 2008). Opposite results have been also reported. Sjöland et al. (1999), Järvinen et al. (2003) and Falcoz et al. (2006) concluded that HRQoL improved among both male and female CABG patients up to two years after the

intervention. Although the reported improvement has been seen both in scores measuring either physical or mental health, male patients have scored significantly better on physical functioning (Koch et al. 2004, Gjejlo et al. 2006) but also in mental health (Vaccarino et al. 2003, Phillips Bute et al. 2003, Lindquist et al. 2003). The results of the present study concur with earlier reports. We found that female patients improved significantly after CABG and that the initial improvement in HRQoL persisted up to 18 months postoperatively despite subsequent stabilization between 6 months and 18 months. Although the mean 15D score of female patients was lower at baseline than that of males, females improved their HRQoL more clearly and the difference in comparison with male patients diminished, becoming insignificant during follow-up. Female patients even maintained a better positive trend than males on dimensions characterizing general well-being, i.e. discomfort and symptoms, distress and vitality.

Our study established poorer HRQoL of females at baseline before surgery. The most significant reason for this may be the difference (mean four years) in age between females and males at the time of admission. Female patients also had more co-morbidity, such as diabetes and they underwent the operation more often on grounds of unstable angina than did males (Study I). Overall co-morbidity was still quite even: NYHA class 3–4 in males 59.8% vs. in 69.8% in females ($p=0.189$); 3-VD 87.4% vs. 77.8% ($p=0.069$); LM >50% 33.5% vs. 33.3% ($p=1.000$); cerebral vascular disease 6.7% vs. 14.3% ($p=0.069$); CHF 3.3% vs. 4.8% ($p=0.704$) (unpublished details from the original data). In light of this, difference in age seemed to be the most significant factor having an impact on the poorer HRQoL of females in our CABG patient material and underlying CAD of greater severity in women than in men only partly explained the difference.

HRQoL determined by the 15D consists after all of 15 dimensions. Each of them has an important effect on the total score. The data from Study I (base material of Figure 2) reveals, that male and female patients differed before the operation significantly on the dimensions moving (p -value for difference in favor of male patients 0.011), breathing ($p<0.001$), discomfort ($p=0.001$) and depression ($p=0.047$). At six months a difference was seen only in moving ($p=0.042$), whereas at 18 months male patients scored better in moving ($p=0.003$), breathing ($p=0.002$) and depression ($p=0.047$). Thus, male CABG patients improved better in physical functioning dimensions of the 15D. This finding agrees quite well with earlier findings of changes in HRQoL between genders (Vaccarino et al. 2003, Phillips Bute et al. 2003, Lindquist et al. 2003, Koch et al. 2004, Falcoz et al. 2006, Gjejlo et al. 2008). Our results refer also indirectly to a poorer outcome of female CABG patients regarding symptoms of

CAD, if we can assume that ease in breathing best reflects symptoms of CAD when the 15D is used as a measure.

Vaccarino and co-authors emphasized cultural and social aspects associated with female gender, which may have an impact on HRQoL. According to Vaccarino female patients consistently reported poorer health than men. However, this is difficult to confirm with the data of the present study. Without penetrating deeper into the progress of CAD after CABG and without invasive examinations (i.e. angiography of coronary arteries) we cannot derive and reach conclusions on less complete revascularization and higher graft occlusion rates as Vaccarino and co-writers conclude (2003). It may be easier to concur with Phillips Bute et al. (2003) that women's HRQoL may be less related to cardiac health than in men. Therefore female patients and especially their HRQoL may be less responsive to cardiac interventions.

6.6 Poorer HRQoL outcome in older ages

Besides gender related positive change of HRQoL we identified a significant improvement of HRQoL in different age groups. Patients >75 years old had significantly poorer level of HRQoL than younger patients besides preoperatively ($p < 0.001$) but also at 6 months ($p = 0.003$) and at 18 months ($p < 0.001$). Our finding of poorer HRQoL in older ages is comparable to findings reported by Järvinen et al. (2003), where the authors found that both the preoperative PCS and the MCS of patients >75 years was lower than in younger age groups. We found that HRQoL improved significantly in all three age groups (<65 years, 65–74 years and >75 years) from preoperative level until the first postoperative control at 6 months. From 6 months onwards HRQoL declined in all age groups but among the oldest patients the change was more dramatic and statistically more significant than in younger ages. The mean 15D score of these patients even reverted to a slightly lower level than before surgery.

It is also important to notice that the number of individual dimensions with positive change declined with age. As patients <65 years improved on seven dimensions and patients between 65–74 years on three dimensions during the first six months, patients in the oldest age group improved on only two dimensions during the same follow-up.

Earlier studies from the 1990's by Glower et al. (1992) and Kumar et al. (1995) in which QoL was assessed through changing functional status revealed improved QoL outcome in patients >80 years. Later on Fruitman et al. (1999) and Conaway et al. (2003) reported a positive change in QoL in older ages during a follow-up

from 12 to 16 months. In Fruitman's study patients older than 80 years achieved even at least on a level of HRQoL equal to that of general population >65 years. The patients in that study fared better than the reference population in domains such as limitations in physical or emotional health, emotional well-being and social functioning. In Järvinen's study (2003) patients >75 years improved their overall HRQoL but improvement was less marked in PCS scoring ($p=0.042$) and in MCS scoring ($p=0.048$) than among younger patients in a follow-up of 12 months. Thus, our finding of positive progress in HRQoL among patients >75 years concurs with earlier studies but only at the beginning of the recovery phase. Unfortunately, studies mentioned afore do not show how lasting the detected improvement of HRQoL in older patients was because the patients were usually checked only once after the baseline examination before treatment. According to our study, HRQoL has a two-sloped development in all ages, also in older ages even in a mid-term follow-up.

The Achilles' heel in the recovery of older patients seems to be a slower and poorer recovery of physical functioning (Järvinen et al. 2003, Conaway et al. 2003, Markou et al. 2008), although recovery from angina related symptoms is similar to that among younger patients (Markou et al. 2008). In our study older patients achieved good and long-lasting improvement in breathing (p -value for change between preoperative state and that at 6 months <0.001) (Study I), which is – as mentioned before – the only dimension having a close relation to angina and thus expressing relief from CAD symptoms also in the oldest patient group. By contrast, patients in the oldest age group did not experience any change in the dimension 'mobility' as patients <75 years did. This may reflect poorer physical recovery of older patients and concerns with earlier reports.

Impaired MCS scoring impacts on the HRQoL of older patients after CABG (Järvinen et al. 2003), although Rumsfeld et al. (2004) concluded that age per 10-year interval predicted rather improvement in mental health during a short follow-up after CABG. In the present study older patients maintained their level on the dimension 'mental' better than both younger age groups, which scored significantly poorer on the dimension under scrutiny. Nevertheless, here we must stress that the dimension 'mental' in the 15D is synonymous with memory and correlation with MCS scoring used in other measures may not be quite analogous. Without structured and repeated memory tests and psychological surveys we cannot confirm if CABG causes decline in mental health outcome.

6.7 The minimum clinically important difference

Changes in HRQoL after treatments of CAD have usually been investigated only statistically. However, we must also assess consequences of the statistical change in clinical practice. Typically, in HRQoL surveys a minimum clinically or quantitatively important difference has not been specified.

The minimum clinically important difference (MCID) is defined as the size of difference or change in the measure that would cause the clinician to change his or her treatment policy (Drummond 2001).

From a statistical point of view MCID is of value in clinical trials to help sample size calculations (Drummond 2001). From a patient's point of view MCID means the minimum level of change that he or she on average can feel as a change. The 15D provides an opportunity to estimate this clinically important or clinically relevant change in the HRQoL of an individual patient or of a group of patients. A change of 0.02–0.03 in the mean 15D score has been observed to be such that people can feel the difference (Sintonen 1994). Actually, besides the 15D MCID has been determined, but not used in surveys of outcome of CAD patients, only in two other measures, i.e. in the Health Utilities Index (HUI) (Furlong et al. 2001) and in the RAND-36 (Hays et al. 1993).

In the study by Kattainen et al. (2005) MCID for improvement of the HRQoL was detected in 26–36% of patients undergoing PTCA or CABG. In the present study proportion of patients with better HRQoL outcome was slightly better as 48.9% of CABG patients and 36.6% of PCI patients achieved clinically relevant improvement by 6 months after the intervention. Moreover, MCID for improvement was detected respectively in 39.8% and 27.6% of the groups by 36 months in our study. When taking into account the difference in the follow-up, 12 months in the study by Kattainen and co-authors and 6 months and 36 months in the present study, the results in the present study corroborate the previous report. However, as much as one fourth of patients in our study experienced clinical impairment during the initial 6-month follow-up and the proportion of patients with negative clinical change in HRQoL increased to one third by 36 months regardless of the treatment option (Study V). Study IV demonstrated moreover that clinically relevant improvement was evident in 46.8% of low-risk patients as assessed with the additive EuroSCORE, in 34.8% of medium-risk patients and in 33.3% of high-risk patients at 36 months. The difference was still insignificant between the risk groups ($p=0.13$). From the risk assessment point of view the finding is that low risk patients may benefit most clearly in their HRQoL after CABG. The finding is not surprising since low risks scored patients are both younger and have less co morbidity.

The finding that half of CABG patients achieved clinically relevant positive change of HRQoL may be acceptable. Contrary to that, the quite high proportion of patients with no change or with change for the worse after the first 6 months' positive recovery may be amazing. However, result is indeed to be expected given that generic instruments consider physical, psychological and social aspects of human life as a whole in the estimation of HRQoL. The normal ageing process affects numerous dimensions by which the instrument used assesses HRQoL. It is also worth considering patients who achieved a 15D score change greater than -0.03 but less than 0.03, which we can call as a 'grey area'. This group of patients included for example individuals with initially high level of HRQoL. Thus, a clinically relevant change in the 15D score may not have been possible to attain despite relief from the symptoms the patients had been treated for. In other words, a patient with a high baseline HRQoL score stays statistically on the base level of HRQoL, although the most desired outcome, life without symptoms of angina, has been reached. The same concerns also preoperatively coexisting or subsequent diseases, which may substantially affect HRQoL and impair it. However, an improvement on at least one important dimension i.e. breathing or in some dimensions may be extraordinarily important for an individual patient although the total 15D score does not show a significant change.

Combining change of the performance state and perceived symptom state with HRQoL we found that a total of 85.9% of CABG patients and 67.5% of PCI patients progressed at least one step in their physical functioning class as long as 36 months after the intervention. Moreover, 68.3% of CABG patients and 58.3% of PCI patients reported that they were asymptomatic in their normal lives after 3 years. Statistically CABG patients advanced compared to PCI patients with respective significances for difference $p < 0.001$ and $p = 0.022$. Of course, comparisons between CABG and PCI groups have to be made carefully because of the non-random design of the present study. Most important still is that a relatively high state of freedom from angina was achieved in both treatment groups. The degree of relief from angina found in the present study correlates with the findings of earlier studies (Parisi et al. 1992, Sim et al. 1995, Pocock et al. 1995, Pocock et al. 1996, Goy et al. 1999, Hueb et al. 1999).

Of CABG patients 21.6% and 25.0% of PCI patients in the present study experienced clinical decline between 0–6 months as the MCID was greater than -0.03. Between preoperative state and 36 months the frequencies were 36.1% and 32.9% respectively (Study IV). Approximately 20% of patients after cardiac surgery are known from the literature not to benefit from heart operations (Duits et al. 1999, Hunt et al. 2000). Neurocognitive deficits have been attributed to negative outcomes with a possible negative impact on HRQoL (Cohen et al. 1999, Newman et al. 2001).

A poor-quality recovery on the days after surgery may predict poor QoL during the first postoperative months (Myles et al. 2001). The role of a chronic stress reaction has also been emphasized (Schelling et al. 2003). The results of the present study are in accordance with previous observations. On the grounds of the measure of HRQoL used it may be impossible to find an unequivocal explanation for the finding. Besides postoperative delirium (Study II) we did not examine postinterventional changes in neurocognitive function. An important explanation for the negative change in such a quite large group of patients may still be the relatively high mean age of the cohort.

6.8 Methodological limitations of HRQoL studies

Contemporary views of HRQoL studies in such a critical illness include broad dimensions and the assessment of patient outcomes after cardiac interventions is well established in the literature (Heyland et al. 2000, Rumsfeld et al. 2001). The use of validated HRQoL instruments has improved the quality and findings of studies, although methodological limitations remain, including short follow-up periods, small sample sizes or lack preinterventional health status measures. Moreover, comparisons of outcomes between the two main options of mechanical interventions, PCI and CABG, are limited due to entry bias. The present study describes the outcome of a “real-world” or a “down-to-earth” cohort with quite a broad patient sample during a long follow-up, which may strengthen the interpretation of the results. On the other hand this study reports the postoperative results of a single center, which may introduce institutional bias.

6.9 Does EuroSCORE predict HRQoL after CABG?

In Study IV we assessed the predictive value of EuroSCORE for HRQoL after CABG. EuroSCORE has been shown to provide a relevant estimate for both short and late outcome after CABG, prolonged length of hospital stay and specific postoperative complications such as renal or respiratory failure and septic complications, as well as the costs of cardiac surgery (Pinna Pintor et al. 2003, Nilsson et al. 2004, Tompoulis et al. 2005). The discriminatory ability of a preoperative risk stratification model to predict HRQoL after coronary bypass surgery has been evaluated only in a few earlier studies. Peric et al. (2005) found that preoperatively high additive value of the EuroSCORE was related to poorer QoL of CABG patients. Although QoL of patients improved during the 6-month follow-up there was no correlation in total

between risk scores and postoperative HRQoL. In the study by Colak et al. (2008) the conclusion was the opposite. Patients with high-risk (additive EuroSCORE >6) improved significantly in most domains of the SF-36 after CABG. The authors concluded that EuroSCORE predicted HRQoL at least in high-risk CABG patients.

In the present study patients with high additive risk score, besides being older, had significantly more preoperative risk factors and co-morbidities. The baseline level of HRQoL in this group was also markedly lower than in the groups with low or medium risk. High-risk patients also had poorer preoperative HRQoL than patients with lower risk, as it was also in the study by Peric et al. (2005). EuroSCORE also predicted longer ICU stay, longer total hospitalization, more morbidity and poorer long-term survival in high-risk patients corroborating earlier findings. EuroSCORE correlated significantly with the mean 15D score of risk groups and thereby with the HRQoL during the whole long-term observation period. Although the mean 15D score and thereby HRQoL of the three risk groups improved as expected after CABG, additive EuroSCORE predicted HRQoL outcome of patients with low risk best. The finding may be predictable because low-risk patients are relatively young and they generally have good preserved left ventricular function and little co-morbidity at the time of the operation. As age per five years from 60 years upwards gives one more point in the additive EuroSCORE, patients >75 years old are directly at least in the medium-risk group and need only two more points to reach the border of high risk. Contrary to that, a greater number of serious co-morbidities is required to reach the high risk level in the low-risk group. As earlier reports have shown the retained HRQoL in higher ages is not as good as in younger ages (Järvinen et al. 2003, Markou et al. 2008) and co-morbidities imply poorer HRQoL of CABG patients (Herliz et al. 1999, Yun et al. 1999, Rumsfeld et al. 2004, Peric et al. 2006). Against this background the poorer HRQoL in the high-risk group is pronounced. The most important adjunctive nominator here is increasing age with quite strong significance for the EuroSCORE. CABG improves HRQoL even for high-scoring patients but for a shorter duration than for low-scoring patients. However, the sensitivity and specificity of the score test were not optimal (Study IV).

From a clinical point of view it is interesting to know how to interpret the risk level for the MCID of HRQoL for which the 15D gives opportunity. Our finding that the best cut-off value for additive EuroSCORE to predict improved HRQoL was 3 fits well with the previous observations of enhanced QoL scores in younger patients with few co-morbidities. Practically the finding signifies that male patients under 75 years and with good preserved LV function and without any other co-morbidity might have the best prospects for good HRQoL after CABG. The same concerns female patients less than 70 years.

6.10 Repeat invasive treatments burden PCI

Study V revealed a larger number of repeat invasive examinations (angiography) and treatments, redo-revascularization with PCI or CABG, after PCI during a follow-up of three years. Of course, CABG, too, was not without repeated interventions but their frequency was significantly lower. This finding has been well documented since the 1990s from the era of PTCA (CABRI Trial Participants 1995, BARI Investigators 1996, Pocock et al. 1995, Pocock et al. 1996) but has continued since the introduction of intracoronary stents (Hueb et al. 1999, Goy et al. 2000, Abizaid et al. 2001, Serruys et al. 2001, SoS Investigators 2002, Rodriquez et al. 2001, Rodriquez et al. 2005, Hannan et al. 2005, Yock et al. 2006, Daemen et al. 2008). The most important cause necessitating repeat revascularization after catheter-based interventions is restenosis, which may be partly resolved by the advent of drug-eluting stents (Cutlip et al. 2004, Chieffo et al. 2007, Kupferwasser et al. 2007, Daemen et al. 2007).

In the present study three quarters of first time repeat angiographies was performed due to new anginal symptoms and one quarter to in aim to check the result of earlier angioplasty. Restenosis was marginally the most common finding, although progression of CAD separate from the treated lesion was found practically equally frequent. Recent AMI caused new anginal symptoms progressively more often when angiography had to be repeated between two and four times. Progression of CAD was also seen whereas the significance of in-stent restenosis declined slightly. Regarding CABG, recent MI was the most important reason for new examinations. The finding was usually progression of the disease either in native vessels or in bypass grafts. These findings are logical, as PCI is usually performed for the treatment of culprit lesion(s). Thus milder coronary plaques, distinct from culprit lesions and with no clinical relevance at the time of treatment, may soon become unstable (Rioufol et al. 2002, Cutlip et al. 2004). In CABG the problem is continuously obstruction or occlusion of grafts, but also progressive CAD in native vessels. To prevent recurrent symptoms from soon appearing a complete revascularization should be the priority. This is optional for any coronary intervention but it may be accomplished more often and more completely by CABG (BARI Investigators 1997, Bair et al. 2007). Regardless of the fact that DES will continue to replace BMS in primary percutaneous interventions, surgery may still be considered more appropriate than stenting with DES in treatment of multivessel CAD (Yang et al. 2007, Yang et al. 2008, Hannan et al. 2008), especially in diabetics (Javaid et al. 2007). Finally, secondary prevention of the CAD may offer the greatest opportunity to improve long-term outcomes after mechanical interventions (Cutlip et al. 2004).

Both PCI and CABG give a fairly good outcome considering survival and relief from angina, but also improvement of HRQoL (Brorsson et al. 2001, Favarato et al. 2004). The initial medical costs for CABG are higher than those for PCI (Weintraub et al. 2004) but the need for repeated procedures may narrow the cost gap between these treatment options later in the follow-up (Weintraub et al. 2004, Stroupe et al. 2006).

6.11 Postoperative delirium impairs HRQoL outcome

The impact of perioperative or postoperative events and complications on HRQoL has not been widely studied (Rumsfeld et al. 2004). Järvinen et al. (2004) concluded that perioperative MI did not have a negative effect on perceived HRQoL during short-term follow-up. Beyond this complication the literature does not contain other perioperative physical complications subjected for research of later HRQoL outcome. The most extensive research on perioperative adverse events has been undertaken from neurological and neurocognitive (i.e. delirium) complications onwards. Postoperative neurobehavioral and neurocognitive complications are associated with prolonged stay in the ICU and with the length of hospitalization after CABG (Roach et al. 1996, Giltay et al. 2006). Neurocognitive complications after cardiac surgery demonstrate significant correlation with impaired QoL and general health status in a long-term follow-up (Newman et al. 2001). Although cardiac surgery with CPB is associated with improvements in HRQoL relative to the preoperative period, the presence of cardiac surgery-related cognitive decline, delirium included, impairs HRQoL in the long-term outcome (Rothenhäusler et al. 2005).

The existing literature shows that the causes of delirious symptoms are multifactorial in origin and the development of delirium involves a complex interaction of precipitating factors as well as peri- and postoperative factors. The incidence of delirium, 6.0%, in the present study is in accordance with earlier studies in which delirium was diagnosed by clinical estimation of deviant behavior. Our approach to the problem was practical, as the diagnosis of delirium presumed not only alteration in behavior but also need for sedative or antipsychotic medical therapy. Independent predictors for delirium (male gender, history of CVD, CHF and age) were common in previous studies, likewise postoperative predictive causes, i.e. pneumonia and LOS. In our patient material patients with later delirium were at greater risk for death according to both additive ($p=0.007$) and logistic ($p=0.005$) EuroSCORE. Postoperative consequences, i.e. respiratory and infection complications, use of ICU resources and total length of hospitalization including

recovery in other medical care units corresponded previous to findings (Wolman et al. 1999, Brown et al. 2002, Bucerius et al. 2004, Giltay et al. 2006) and 36-month survival was significantly poorer among patients with delirium ($p < 0.001$).

HRQoL of patients who developed delirium was significantly lower preoperatively than for patients with normal postoperative course as assessed with the mean 15D score of the group. The difference consisted essentially of poorer scores of dimensions for senses, i.e. seeing and hearing, but also of dimensions for daily life, i.e. eating, speaking and elimination in the delirium patient group. Of course, more advanced age together with concurrent morbidity may also have influenced the mean scores of delirium patients. There was also one exceptional observation, a significantly high prevalence of malignancies, although in remission phase in all cases at the time of cardiac surgery. However, the role of this finding in HRQoL cannot be explained on the basis of data available.

HRQoL advanced as anticipated in patients with uncomplicated neuropsychological outcome. Thus there was a significant improvement during the first 6 months after CABG followed by leveling out until 18 months and stabilization later on. This patient group achieved still better HRQoL even by 18-month control. Contrary to this the HRQoL of delirium patients remained on the preoperative level until 36 months. The only exception were patients with high preoperative 15D score and hence a high level of HRQoL. This group tended rather to decline during the first 6-month period in contrast to 'normal' improvement usually seen in cardiac surgery patients, although the process was reversible. One explanation may be that patients with a basically good standard of HRQoL may be more sensitive to even small dimensional changes and thus experience quite radical deterioration in case of such a severe neuropsychological alteration as delirium is. This finding should be addressed by further studies with a greater number of patients and with a structured and sensitive instrument to assess neurobehavioral complications after CABG. Our study design does not allow estimate further, for example, the role of embolization or other perioperative factors as a primary cause for delirium.

6.12 Future directions

The field of HRQoL research has advanced also in CAD since the first attempts in the 1990s. Studies have mostly been institutional reports with a limited number of patients and generally with a relatively short follow-up. In daily life the usual practice is counseling CAD patients after invasive examination regarding the extent of the anticipated treatment on the basis of the extent and degree of severity of the disease.

Besides general information, discussion with patients also contains an assumption of their morbidity and mortality risk that have to be handled as delicately and gently as possible. Prolonged relief from angina is frequently achievable by invasive treatments. Patients with significant LM stenosis or proximal LAD stenosis can even expect significantly better survival prognosis. However, patients should also be counseled on anticipated changes in HRQoL, both in physical and mental health, after the planned invasive treatment. This assumes not only continuous follow-up of survival, MACE and angina class but also the introduction of a generally accepted and standardized generic instrument for assessing HRQoL preoperatively and during follow-up. By this means the data collected could augment clinical decision-making in choosing the option for the treatment for different patient subgroups and at least in borderline cases. For all CAD patients this advance may lead to identifying who will also have a quality of life benefit from the treatment besides the much expected relief from anginal burden.

7 CONCLUSIONS

On the basis of this study the following conclusions may be drawn:

CABG patients experience a significant improvement in their HRQoL within 6 months after the operation and the effect persists through a mid-term observation time. However, during longer follow-up the HRQoL of patients undergoing invasive treatment tends to decline, especially among older CABG patients.

Postoperative complications, i.e. delirium may exert a negative influence on future HRQoL, which may be seen especially in patients with a relatively high preoperative level of HRQoL.

EuroSCORE, beyond the prediction of postoperative survival, also predicts long-term HRQoL after CABG.

Despite initially more serious preoperative state and more demanding procedure CABG patients achieve an equal level of HRQoL and even better relief from symptoms than PCI patients in mid-term follow-up.

The high probability of need for repeat invasive examinations and revascularization after PCI has to be taken into consideration when choosing an invasive approach for coronary artery diseased patients with multivessel disease.

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APPENDICES

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APPENDIX 1

Studies reporting comparisons between invasive treatment and medical therapy for outcome of CAD patients.

Reference	Design	Time (yrs)	Comment
<i>CABG vs. MT</i>			
VA CABG Cooperative Study Group Takaro et al. 1976	Randomized	2–18	Survival and relief from angina benefit after CABG in LM stenosis. Better relief from angina and better exercise performance among CABG patients during 5 yrs, but equal after 10 yrs of follow-up. Overall survival benefit for CABG. Transient survival benefit for CABG by 18 yrs for high-risk patients.
Peduzzi et al. 1987 VA Study Group 1984, 1992	Randomized	10	Better survival after CABG for patients with low EF and with 3-VD during 10 yrs of follow-up (85% vs. 70%, $p=0.01$).
Passamani et al. 1985	Registry based	6	6-year survival rate 89% after CABG vs. 76% with MT ($p<0.0010$) in 2-VD. Survival benefit for patients with CCS class 3-4 angina and impaired LV-function.
Mock et al. 1988	Randomized	10	Long-term survival benefit from bypass surgery for patients with LV-dysfunction, but equivalent for patients with good reserved EF and mild angina.
Alderman et al. 1990	Meta-analysis	10	Mortality after CABG lower than that with MT at 5 yrs (10.2% vs. 15.8%, $p=0.001$), at 7 seven yrs (15.8% vs. 21.7%, $p<0.001$) and at 10 yrs (26.4% vs. 30.5%, $p=0.03$). The absolute benefit in LM stenosis and in 3-VD. Low risk patients with 1-VD obtain no benefit from surgery compared to MT.
Yusuf et al. 1994	Non-random-ized, prospec-tive	5	In 1-VD no survival advance in 5 yrs for CABG over MT. In 2-VD higher survival rates after CABG. In severe 2-VD and in 3-VD CABG provides consistent survival advantage over MT. For less severe CAD the primary treatment choices are between MT and PTCA.
Mark et al. 1994			
<i>PTCA/PCI vs. MT</i>			
Parisi et al. 1992	Randomized	<1	64% of PTCA patients vs. 46% of MT patients free from angina ($p<0.01$). PTCA patients had better exercise tolerance ($p<0.0001$). Repeat interventions in 16% of cases in the PTCA group.
Hueb et al. 2004	Randomized	1	No difference in cardiac death or acute MI among patients with MVD in CABG, PTCA or MT groups. Additional interventions after one-year follow-up in 8.3% of patients with MT, 13.3% with PTCA and 0.5% with CABG. Freedom from angina in 46%, 79% and 88% respectively ($p<0.0001$).
Katrisis and Ioannidis 2005	Meta-analysis	1 – 7	No significant difference was seen between PCI and MT in patients with stable CAD regarding mortality, cardiac death and MI, neither in repeats CABG or PCI. A possible survival benefit for PCI in patients with relatively recent MI (RR 0.40, 95% CI 0.17–0.95).

APPENDIX 2

CABG versus PCI in the treatment of MVD.

Reference	Design	Time (yrs)	Comment
<i>CABG vs. PTCA/PCI for MVD</i>			
CABRI Trial Participants 1995	Randomized, multicenter	1	Mortality 2.7% and 3.9% for CABG and PTCA groups. Reinterventions after PTCA or CABG 33.6% vs. 6.5% (RR 5.23, 95% CI 3.90–7.03, p<0.001). PTCA patients had more angina (RR 1.54, 95% CI 1.09–2.16, p=0.012); association was significant in females.
BARI Investigators 1996	Randomized, multicenter	5	In-hospital mortality 1.1% and 1.3% (NS). More perioperative MI after CABG (4.6% vs. 2.1%, p<0.01). No difference in 5-year survival. Additional revascularization required for 54% of PTCA patients and 8% of CABG patients. Survival difference in diabetics, 65.5% and 80.6% respectively (p=0.003).
RITA Study Pocock et al. 1996 Henderson et al. 1998	Randomized, multicenter	5	No difference in long-term survival or mortality. Subsequent CABG in 26% vs. 13% and subsequent PTCA in 27% vs. 9% of PTCA and CABG patients respectively. Prevalence of angina higher in the PTCA group (p<0.001).
Pocock et al. 1995	Meta-analysis	3	Total mortality and cardiac death equal between CABG and PTCA. The prevalence of angina higher in the PTCA group at one year (RR 1.56, 95% CI 1.30–1.88), but by 3 yrs the difference diminished (RR 1.22, 95% CI 0.09–1.54). Repeat interventions 17.8% (PTCA) vs. 3.3% (CABG).
Sim et al. 1995	Meta-analysis	3	Mortality 3.7% in CABG patients and 3.9% in PTCA patients by 3 yrs (NS). CABG patients more likely free of angina (80.7% vs. 73.1%, OR 1.57, 95% CI 1.32–1.87, p<0.00001). The frequency of subsequent CABG 1.0% among CABG patients and 19.7% in PTCA patients and subsequent PTCA 6.0% vs. 22.9% respectively.
<i>CABG vs. stent-assisted PCI</i>			
Serruys et al. 2001	Randomized	1	The rate of mortality (2.8% after surgery vs. 2.5% after PCI), cerebral vascular accidents (2.0% vs. 1.5%) and MI (4.0% vs. 5.3%) was equal. Need for repeated revascularization 3.5% in the CABG group and 16.8% in the PCI group (RR 5.52, 95% CI 3.59–8.49, p<0.001).
SoS Study SoS Investigators 2002 Zhang et al. 2003 Booth et al. 2008	Randomized		The incidence of death or Q-wave MI similar (CABG 10%, PCI 9%). Fewer deaths in the CABG group (5% vs. 2%, p=0.01). 21% of PCI patients and 6% of CABG patients required additional revascularization (RR 3.85, 95% CI 2.56–5.79, p<0.0001). 6-years mortality 10.9% in the PCI group vs. 6.8% in the CABG group (HR 1.6, 95% CI 1.08–2.55, p=0.022), with evidence of a continuing survival advantage for CABG patients, which deviates from results of other stent-versus-CABG studies.

ERACI II Trial Rodriguez et al. 2001 Rodriguez et al. 2005	Randomized	1.5 – 5	Frequency of MACE in 30 days 3.6% after PCI vs. 12.3% after CABG (p=0.002) and death 0.9% vs. 5.7% (p<0.013). Survival at the mean of 18.5 months of follow-up 96.9% vs. 92.5% respectively (p<0.017). After 5 years PCI and CABG patients had similar rates of survival (92.8% vs. 88.4%) and freedom from non-fatal MI 97.3% vs. 94%, p=0.16). Freedom of repeat PCI or CABG (71.5% vs. 92.4%, p=0.0002) and from MACE (65.3% vs. 76.4%, p=0.013) was lower in PCI patients than after CABG.
Hannan et al. 2005	Registry based	3	CABG patients were older and had more preinterventional risk factors than PCI patients. 7.8% of patients with stent underwent subsequent CABG and 27.3% underwent repeat PCI. Frequencies were 0.3% and 4.6% in the CABG group respectively (p<0.001).
Daemen et al 2008	Meta-analysis	5	The cumulative incidence of death, MI and stroke was 16.7% in PCI patients and 19.9% in CABG patients (p=0.69). Repeat revascularization was needed more frequently after PCI than after CABG (29% vs. 7.9%). MACE occurred more often in the PCI group than in the CABG group 39.2% and 23.0%, P<0.001). Long-term safety profile similar between the groups.
Abizaid et al. 2001 CABG vs. DES Javadi et al. 2007	Randomized Observational	1	PCI vs. CABG for MVD in diabetics. Event-free survival rate 64.3% and 84.4% (p<0.001) among the groups because of a higher incidence of repeat interventions in the PCI group.
Yang et al. 2007	Observational	2	Rate of MACE in 2-VD 9.7% for CABG patients vs. 21.2% for PCI patients (p<0.001) and 10.8% vs. 28.4% in 3-VD (p<0.001). CABG resulted in improved MACE in 2-VD and in 3-VD and primarily in patients with underlying diabetes.
New York State Register Study Hannan et al. 2008	Registry based	1.5	Higher early morbidity after CABG than PCI with DES (3.9% vs. 0.8%, p=0.03). The incidence of MACE similar in both groups (5.6% vs. 6.3%, p=0.84), but PCI with DES afforded a higher need for repeat revascularization (10.4% vs. 2.8%, p=0.03)
SYNTAX Trial Serruys et al. 2009	Randomized	1	Lower rates of death and death for MI after CABG than after PCI with DES both in 2-VD and 3-VD. Survival 94.0% vs. 92.7% (p=0.03) in 2-VD and 96.0% vs. 94.6% (p=0.003) in 3-VD. The rate of repeat PCI after initial PCI with DES 28.4% vs. 5.1% after initial CABG and repeat revascularization with CABG 2.2% and 0.1% (p<0.001) respectively.
LAD as the target vessel Goy et al. 1999	Randomized	5	Rate of MACE 17.8% in the PCI group vs. 12.4% in the CABG group (p=0.002). Repeat revascularization was needed in 13.5% vs. 5.9% among the groups respectively. No difference in the rates of death or MI, but stroke was more likely to occur after CABG (2.2% vs. 0.6%, p=0.003).
			PTCA or CABG using the LITA. No difference in survival. Freedom from angina in 86% of CABG patients and 43% of PTCA patients at 2.5 yrs of follow-up. Repeat revascularization 9% vs. 38% within 5 yrs among the groups respectively. 91% vs. 62% of patients totally free of events at 5 yrs (p=0.0001).

MASS II Trial Hueb et al. 1999	Randomized	5	The cumulative event-free rates for CABG, PTCA and MT 98.6%, 63.9% and 88.9% (p=0.001). Less redo-revascularization after CABG than after PTCA. Better relief from angina achieved with invasive treatment than with MT.
Goy et al. 2000	Randomized	< 1	No difference in rates of MI or death. Perceived functional status equal. However, 31% of PCI patients vs. 7% of CABG patients needed additional revascularization (p<0.01).

APPENDIX 3

Quality of life questionnaire (15D©)

Please read through all the alternative responses to each question before placing a cross (x) against the alternative which best describes your present health status. Continue through all 15 questions in this manner, giving only one answer to each.

QUESTION 1. MOBILITY

- 1 () I am able to walk normally (without difficulty) indoors, outdoors and on stairs.
- 2 () I am able to walk without difficulty indoors, but outdoors and/or on stairs I have slight difficulties.
- 3 () I am able to walk without help indoors (with or without an appliance), but outdoors and/or on stairs only with considerable difficulty or with help from others.
- 4 () I am able to walk indoors only with help from others.
- 5 () I am completely bed-ridden and unable to move about.

QUESTION 2. VISION

- 1 () I see normally, i.e. I can read newspapers and TV text without difficulty (with or without glasses).
- 2 () I can read papers and/or TV text with slight difficulty (with or without glasses).
- 3 () I can read papers and/or TV text with considerable difficulty (with or without glasses).
- 4 () I cannot read papers or TV text either with glasses or without, but I can see enough to walk about without guidance.
- 5 () I cannot see enough to walk about without a guide, i.e. I am almost or completely blind.

QUESTION 3. HEARING

- 1 () I can hear normally, i.e. normal speech (with or without a hearing aid).
- 2 () I hear normal speech with a little difficulty.
- 3 () I hear normal speech with considerable difficulty; in conversation I need voices to be louder than normal.
- 4 () I hear even loud voices poorly; I am almost deaf.
- 5 () I am completely deaf.

QUESTION 4. BREATHING

- 1 () I am able to breathe normally, i.e. with no shortness of breath or other breathing difficulty.
- 2 () I have shortness of breath during heavy work or sports, or when walking briskly on flat ground or slightly uphill.
- 3 () I have shortness of breath when walking on flat ground at the same speed as others my age.
- 4 () I get shortness of breath even after light activity, e.g. washing or dressing myself.
- 5 () I have breathing difficulties almost all the time, even when resting.

QUESTION 5. SLEEPING

- 1 () I am able to sleep normally, i.e. I have no problems with sleeping.
- 2 () I have slight problems with sleeping, e.g. difficulty in falling asleep, or sometimes waking at night.
- 3 () I have moderate problems with sleeping, e.g. disturbed sleep, or feeling I have not slept enough.
- 4 () I have great problems with sleeping, e.g. having to use sleeping pills often or routinely, or usually waking at night and/or too early in the morning.
- 5 () I suffer severe sleeplessness, e.g. sleep is almost impossible even with full use of sleeping pills, or staying awake most of the night.

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QUESTION 6. EATING

- 1 () I am able to eat normally, i.e. with no help from others.
- 2 () I am able to eat by myself with minor difficulty (e.g. slowly, clumsily, shakily, or with special appliances).
- 3 () I need some help from another person in eating.
- 4 () I am unable to eat by myself at all, so I must be fed by another person.
- 5 () I am unable to eat at all, so I am fed either by tube or intravenously.

QUESTION 7. SPEECH

- 1 () I am able to speak normally, i.e. clearly, audibly and fluently.
- 2 () I have slight speech difficulties, e.g. occasional fumbling for words, mumbling, or changes of pitch.
- 3 () I can make myself understood, but my speech is e.g. disjointed, faltering, stuttering or stammering.
- 4 () Most people have great difficulty understanding my speech.
- 5 () I can only make myself understood by gestures.

QUESTION 8. ELIMINATION

- 1 () My bladder and bowel work normally and without problems.
- 2 () I have slight problems with my bladder and/or bowel function, e.g. difficulties with urination, or loose or hard bowels.
- 3 () I have marked problems with my bladder and/or bowel function, e.g. occasional 'accidents', or severe constipation or diarrhea.
- 4 () I have serious problems with my bladder and/or bowel function, e.g. routine 'accidents', or need of catheterization or enemas.
- 5 () I have no control my bladder and/or bowel function.

QUESTION 9. USUAL ACTIVITIES

- 1 () I am able to perform my usual activities (e.g. employment, studying, housework, free-time activities) without difficulty.
- 2 () I am able to perform my usual activities slightly less effectively or with minor difficulty.
- 3 () I am able to perform my usual activities much less effectively, with considerable difficulty, or not completely.
- 4 () I can only manage a small proportion of my previously usual activities.
- 5 () I am unable to manage any of my previously usual activities.

QUESTION 10. MENTAL FUNCTION

- 1 () I am able to think clearly and logically, and my memory functions well.
- 2 () I have slight difficulties in thinking clearly and logically, or my memory sometimes fails me.
- 3 () I have marked difficulties in thinking clearly and logically, or my memory is somewhat impaired.
- 4 () I have great difficulties in thinking clearly and logically, or my memory is seriously impaired.
- 5 () I am permanently confused and disoriented in place and time.

QUESTION 11. DISCOMFORT AND SYMPTOMS

- 1 () I have no physical discomfort or symptoms, e.g. pain, ache, nausea, itching etc.
- 2 () I have mild physical discomfort or symptoms, e.g. pain, ache, nausea itching etc.
- 3 () I have marked physical discomfort or symptoms, e.g. pain, ache, nausea itching etc.
- 4 () I have severe physical discomfort or symptoms, e.g. pain, ache, nausea itching etc.
- 5 () I have unbearable physical discomfort or symptoms, e.g. pain, ache, nausea itching etc.

QUESTION 12. DEPRESSION

- 1 () I do not feel at all sad, melancholic or depressed.
- 2 () I feel slightly sad, melancholic or depressed.
- 3 () I feel moderately sad, melancholic or depressed.
- 4 () I feel very sad, melancholic or depressed.
- 5 () I feel extremely sad, melancholic or depressed.

QUESTION 13. DISTRESS

- 1 () I do not feel at all anxious, stressed or nervous.
- 2 () I feel slightly anxious, stressed or nervous.
- 3 () I feel moderately anxious, stressed or nervous.
- 4 () I feel very anxious, stressed or nervous.
- 5 () I feel extremely anxious, stressed or nervous.

QUESTION 14. VITALITY

- 1 () I feel healthy and energetic.
- 2 () I feel slightly weary, tired or feeble.
- 3 () I feel moderately weary, tired or feeble.
- 4 () I feel very weary, tired or feeble, almost exhausted.
- 5 () I feel extremely weary, tired or feeble, totally exhausted.

QUESTION 15. SEXUAL ACTIVITY

- 1 () My state of health has no adverse effect on my sexual activity.
- 2 () My state of health has slight effect on my sexual activity.
- 3 () My state of health has a considerable effect on my sexual activity.
- 4 () My state of health makes sexual activity almost impossible.
- 5 () My state of health makes sexual activity impossible.

APPENDIX 4

15D©: kyselylomake

1. LIIKUNTAKYKY

- | | |
|---|---|
| 1 | Pystyn kävelemään normaalisti (vaikeuksitta) sisällä, ulkona ja portaissa. |
| 2 | Pystyn kävelemään vaikeuksitta sisällä, mutta ulkona ja/tai portaissa on pieniä vaikeuksia |
| 3 | Pystyn kävelemään ilman apua sisällä (apuvälinein tai ilman), mutta ulkona ja/tai portaissa melkoin vaikeuksin tai toisen avustamana. |
| 4 | Pystyn kävelemään sisälläkin vain toisen avustamana. |
| 5 | Olen täysin liikuntakyvytön ja vuoteenoma |

2. NÄKÖ

- | | |
|---|---|
| 1 | Näen normaalisti eli näen lukea lehteä ja TV:n tekstejä vaikeuksitta (silmälaseilla tai ilman). |
| 2 | Näen lukea lehteä ja/tai TV:n tekstejä pienin vaikeuksin (silmälaseilla tai ilman). |
| 3 | Näen lukea lehteä ja/tai TV:n tekstejä huomattavin vaikeuksin (silmälaseilla tai ilman). |
| 4 | En näe lukea lehteä enkä TV:n tekstejä ilman silmälaseja tai niiden kanssa, mutta näen kulkea ilman opasta. |
| 5 | En näe kulkea oppaatta eli olen lähes tai täysin sokea. |

3. KUULO

- | | |
|---|---|
| 1 | Kuulen normaalisti eli kuulen hyvin normaalia puheääntä (kuulokojeella tai ilman). |
| 2 | Kuulen normaalia puheääntä pienin vaikeuksin. |
| 3 | Minun on melko vaikea kuulla normaalia puheääntä, keskustelussa on käytettävä normaalia kovempaa puheääntä. |
| 4 | Kuulen kovaakin puheääntä heikosti; olen melkein kuuro. |
| 5 | Olen täysin kuuro. |

4. HENGITYS

- | | |
|---|---|
| 1 | Pystyn hengittämään normaalisti eli minulla ei ole hengenahdistusta eikä muita hengitysvaikeuksia. |
| 2 | Minulla on hengenahdistusta raskaassa työssä tai urheillessa, reippaassa kävelyssä tasamaalla tai lievässä ylämäessä. |
| 3 | Minulla on hengenahdistusta, kun kävelen tasamaalla samaa vauhtia kuin muut ikäiseni. |
| 4 | Minulla on hengenahdistusta pienenkin rasituksen jälkeen, esim. peseytyessä tai pukeutuessa. |
| 5 | Minulla on hengenahdistusta lähes koko ajan, myös levossa. |

5. NUKKUMINEN

- | | |
|---|---|
| 1 | Nukun normaalisti eli minulla ei ole mitään ongelmia unen suhteen. |
| 2 | Minulla on lieviä uniongelmia, esim. nukahtamisvaikeuksia tai satunnaista yöheräilyä. |
| 3 | Minulla on melkoisia uniongelmia, esim. nukun levottomasti tai uni ei tunnu riittävältä. |
| 4 | Minulla on suuria uniongelmia, esim. joudun käyttämään usein tai säännöllisesti unilääkettä, herään säännöllisesti yöllä ja/tai aamuisin liian varhain. |
| 5 | Kärsin vaikeasta unettomuudesta, esim. unilääkkeiden runsaasta käytöstä huolimatta nukkuminen on lähes mahdotonta, valvon suurimman osan yöstä. |

6. SYÖMINEN

- | | |
|---|---|
| 1 | Pystyn syömään normaalisti eli itse ilman mitään vaikeuksia. |
| 2 | Pystyn syömään itse pienin vaikeuksin (esim. hitaasti, kömpelösti, vavisten tai erityisapuneuvoin). |
| 3 | Tarvitsen hieman toisen apua syömisessä. |
| 4 | En pysty syömään itse lainkaan, vaan minua pitää syöttää. |
| 5 | En pysty syömään itse lainkaan, vaan minulle pitää antaa ravintoa letkun avulla tai suonensisäisesti. |

7. PUHUMINEN

- | | |
|---|--|
| 1 | Pystyn puhumaan normaalisti eli selvästi, kuuluvasti ja sujuvasti. |
| 2 | Puhuminen tuottaa minulle pieniä vaikeuksia, esim. sanoja on etsittävä tai ääni ei ole riittävän kuuluva tai se vaihtaa korkeutta. |
| 3 | Pystyn puhumaan ymmärrettävästi, mutta katkonaisesti, ääni vavisten, sammaltaen tai änkyttäen. |
| 4 | Muilla on vaikeuksia ymmärtää puhettani. |
| 5 | Pystyn ilmaisemaan itseäni vain elein. |

8. ERITYSTOIMINTA

- | | |
|---|---|
| 1 | Virtsarakkoni ja suolistoni toimivat normaalisti ja ongelmitta. |
| 2 | Virtsarakkoni ja/tai suolistoni toiminnassa on lieviä ongelmia, esim. minulla on virtsaamisvaikeuksia tai kova tai löysä vatsa. |
| 3 | Virtsarakkoni ja/tai suolistoni toiminnassa on melkoisia ongelmia, esim. minulla on satunnaisia virtsanpidätysvaikeuksia tai vaikea ummetus tai ripuli. |
| 4 | Virtsarakkoni ja/tai suolistoni toiminnassa on suuria ongelmia, esim. minulla on säännöllisesti "vahinkoja" tai peräruiskeiden tai katetroinnin tarvetta. |
| 5 | En hallitse lainkaan virtsaamista ja/tai ulostamista. |

9. TAVANOMAISET TOIMINNOT

- | | |
|---|--|
| 1 | Pystyn suoriutumaan normaalisti tavanomaisista toiminnoista (esim. ansiotyö, opiskelu, kotityö, vapaa-ajan toiminnot). |
| 2 | Pystyn suoriutumaan tavanomaisista toiminnoista hieman alentuneella teholla tai pienin vaikeuksin. |
| 3 | Pystyn suoriutumaan tavanomaisista toiminnoista huomattavasti alentuneella teholla tai huomattavin vaikeuksin tai vain osaksi. |
| 4 | Pystyn suoriutumaan tavanomaisista toiminnoista vain pieneltä osin. |
| 5 | En pysty suoriutumaan lainkaan tavanomaisista toiminnoista. |

10. HENKINEN TOIMINTA

- | | |
|---|--|
| 1 | Pystyn ajattelemaan selkeästi ja johdonmukaisesti ja muistini toimii täysin moitteettomasti. |
| 2 | Minulla on lieviä vaikeuksia ajatella selkeästi ja johdonmukaisesti, tai muistini ei toimi täysin moitteettomasti. |
| 3 | Minulla on melkoisia vaikeuksia ajatella selkeästi ja johdonmukaisesti, tai minulla on jonkin verran muistinmenetystä. |
| 4 | Minulla on suuria vaikeuksia ajatella selkeästi ja johdonmukaisesti, tai minulla on huomattavaa muistinmenetystä. |
| 5 | Olen koko ajan sekaisin ja vailla ajan tai paikan tajua. |

11. VAIVAT JA OIREET

- | | |
|---|--|
| 1 | Minulla ei ole mitään vaivoja tai oireita, esim. kipua, särkyä, pahoinvointia, kutinaa jne. |
| 2 | Minulla on lieviä vaivoja tai oireita, esim. lievää kipua, särkyä, pahoinvointia, kutinaa jne. |
| 3 | Minulla on melkoisia vaivoja tai oireita, esim. melkoista kipua, särkyä, pahoinvointia, kutinaa jne. |
| 4 | Minulla on voimakkaita vaivoja tai oireita, esim. voimakasta kipua, särkyä, pahoinvointia, kutinaa jne. |
| 5 | Minulla on sietämättömiä vaivoja ja oireita, esim. sietämätöntä kipua, särkyä, pahoinvointia, kutinaa jne. |

12. MASENTUNEISUUS

- | | |
|---|--|
| 1 | En tunne itseäni lainkaan surulliseksi, alakuloiseksi tai masentuneeksi. |
| 2 | Tunnen itseni hieman surulliseksi, alakuloiseksi tai masentuneeksi. |
| 3 | Tunnen itseni melko surulliseksi, alakuloiseksi tai masentuneeksi. |
| 4 | Tunnen itseni erittäin surulliseksi, alakuloiseksi tai masentuneeksi. |
| 5 | Tunnen itseni äärimmäisen surulliseksi, alakuloiseksi tai masentuneeksi. |

13. AHDISTUNEISUUS

- | | |
|---|---|
| 1 | En tunne itseäni lainkaan ahdistuneeksi, jännittyneeksi tai hermostuneeksi. |
| 2 | Tunnen itseni hieman ahdistuneeksi, jännittyneeksi tai hermostuneeksi. |
| 3 | Tunnen itseni melko ahdistuneeksi, jännittyneeksi tai hermostuneeksi. |
| 4 | Tunnen itseni erittäin ahdistuneeksi, jännittyneeksi tai hermostuneeksi. |
| 5 | Tunnen itseni äärimmäisen ahdistuneeksi, jännittyneeksi tai hermostuneeksi. |

14. ENERGISYYS

- | | |
|---|--|
| 1 | Tunnen itseni terveeksi ja elinvoimaiseksi. |
| 2 | Tunnen itseni hieman uupuneeksi, väsyneeksi tai voimattomaksi. |
| 3 | Tunnen itseni melko uupuneeksi, väsyneeksi tai voimattomaksi. |
| 4 | Tunnen itseni erittäin uupuneeksi, väsyneeksi tai voimattomaksi, lähes "loppuun palaneeksi". |
| 5 | Tunnen itseni äärimmäisen uupuneeksi, väsyneeksi tai voimattomaksi, täysin "loppuun palaneeksi". |

15. SUKUPUOLIELÄMÄ

- | | |
|---|---|
| 1 | Terveystilani ei vaikeuta mitenkään sukupuolielämääni. |
| 2 | Terveystilani vaikeuttaa hieman sukupuolielämääni. |
| 3 | Terveystilani vaikeuttaa huomattavasti sukupuolielämääni. |
| 4 | Terveystilani tekee sukupuolielämäni lähes mahdottomaksi. |
| 5 | Terveystilani tekee sukupuolielämäni mahdottomaksi. |

APPENDIX 5

Frågor angående livskvalitet (15D©)

1. RÖRELSEFÖRMÅGA

- 1 () Jag kan gå normalt (utan svårigheter) inomhus, utomhus och i trappor.
- 2 () Jag kan gå utan svårigheter inomhus, men utomhus och/eller i trappor har jag lite svårigheter.
- 3 () Jag kan gå utan svårigheter inomhus (med hjälpmedel eller utan), men utomhus och/eller i trappor har jag ganska mycket svårigheter eller behöver hjälp av en annan person.
- 4 () Jag kan gå även inomhus endast med hjälp av en annan person.
- 5 () Jag är helt rörelsehindrad och sängbunden.

2. SYN

- 1 () Jag har normal syn, dvs. jag ser att läsa tidning och TV:s texter utan svårigheter.
- 2 () Jag ser att läsa tidning och TV:s texter med lite svårigheter (med glasögon eller utan).
- 3 () Jag ser att läsa tidning och/eller TV:s texter med betydande svårigheter (med glasögon eller utan).
- 4 () Jag ser inte, varken med eller utan glasögon, att läsa tidning eller TV:s texter, men jag klarar mig (kunde klara mig) utan personlig assistent.
- 5 () Jag klarar (skulle inte klara) mig inte utan assistent, dvs. jag är nästan eller helt blind.

3. HÖRSEL

- 1 () Jag hör normalt, dvs. jag hör väl normal talröst (med hörapparat eller utan).
- 2 () Jag hör normal talröst med små svårigheter.
- 3 () Jag hör normal talröst med betydliga svårigheter, under samtal krävs högre talröst än normalt.
- 4 () Jag hör svagt även hög talröst; jag är nästan döv.
- 5 () Jag är helt döv.

4. ANDNING

- 1 () Jag andas normalt, dvs. jag har inte andnöd eller andra andningsbesvär.
- 2 () Jag får andnöd under tungt arbete eller sport, rask gång på slä mark eller i lindrig uppförsläge.
- 3 () Jag har andnöd under gång tillsammans med jämnåriga på slät mark.
- 4 () Jag får andnöd även under lindrig ansträngning, tex. under tvättning och påklädning.
- 5 () Jag har andnöd nästan hela tiden, även i vila.

5. SÖMN

- 1 () Jag sover normalt, dvs. jag har inga problem med sömnen.
- 2 () Jag har lindriga sömnproblem, tex. jag har svårt att somna eller jag vaknar sporadiskt under natten.
- 3 () Jag har betydliga sömnproblem, tex. jag sover oroligt, det känns att jag inte får tillräckligt sömn.
- 4 () Jag har stora sömnproblem, tex. jag är tvungen att använda sömnmedicin ofta eller regelbundet, jag vaknar regelbundet under natten och/eller vaknar för tidigt på morgonen.
- 5 () Jag lider av svår sömnlöshet, tex. trots rikligt användande av sömnmedicin är det nästan omöjligt att sova, jag vakar största delen av natten

6. ÄTANDE

- 1 () Jag kan äta normalt, dvs. själv utan svårigheter.
- 2 () Jag kan äta själv med små svårigheter (tex. långsamt, klumpigt, darrande eller med hjälp av specialhjälpmedel).
- 3 () Jag behöver en aning hjälp av en annan person när jag äter.
- 4 () Jag kan inte alls äta själv, någon måste mata mig.
- 5 () Jag kan inte alls äta själv, jag måste matas med hjälp av slang eller med intravenös näring.

7. TAL

- 1 () Jag kan tala normalt, dvs. klart, tydligt och flytande.
- 2 () Jag har små svårigheter med tal, tex. jag måste söka orden eller rösten är inte tillräckligt tydlig eller den ändrar tonhöjd.
- 3 () Jag kan tala förståeligt, men stapplande, darrande, läspande eller stammande.
- 4 () Andra personer har svårt att förstå mitt tal.
- 5 () Jag kan uttrycka mig endast med gester.

8. UTSÖNDRING

- 1 () Min urinblåsa och tarm fungerar problemfritt.
- 2 () Jag har små problem med min urinblåsa- och/eller tarmfunktion, tex. jag har urineringsproblem eller hård eller lös mage.
- 3 () Jag har betydande problem med min urinblåsa- och/eller tarmfunktion, tex. jag har sporadiska inkontinensbesvär eller svår förstoppning eller diarre'.
- 4 () Jag har stora problem med min urinblåsa- och/eller tarmfunktion, tex. jag har regelbundet "misstag" eller behov av laverang eller katetrisering.
- 5 () Jag har ingen kontroll över min urinblåsa- och/eller tarmfunktion.

9. VANLIGA FUNKTIONER

- 1 () Jag klarar mig normalt med vanliga funktioner (tex. arbete, studier, hemsysslor, fritids-intressen).
- 2 () Jag klarar mina vanliga funktioner med en aning sänkt förmåga eller med små svårigheter.
- 3 () Jag klarar mina vanliga funktioner med betydligt sänkt förmåga eller med betydande svårigheter eller endast delvis.
- 4 () Jag klarar endast en liten del av mina vanliga funktioner.
- 5 () Jag klarar inte alls mina vanliga funktioner.

10. MENTAL FUNKTION

- 1 () Jag kan tänka klart och konsekvent, mitt minne fungerar felfritt.
- 2 () Jag har lindriga svårigheter att tänka klart och konsekvent, mitt minne fungerar inte helt elfritt.
- 3 () Jag har betydande svårigheter att tänka klart och konsekvent, jag lider i någon mån av minnesförlust.
- 4 () Jag har stora svårigheter att tänka klart och konsekvent, jag lider av betydande minnesförlust.
- 5 () Jag är helt förvirrad och jag har inget begrepp om tid och rum.

11. BESVÄR OCH SYMPTOM

- 1 () Jag lider inte av några besvär eller symptom, tex. smärta, värk, illamående, klåda osv.
- 2 () Jag lider av lindriga besvär eller symptom, tex. lindrig smärta, värk, illamående, klåda osv.
- 3 () Jag lider av betydande besvär eller symptom, tex. betydande smärta, värk, illamående, klåda osv.
- 4 () Jag lider av svåra besvär eller symptom, tex. svår smärta, värk, illamående, klåda osv.
- 5 () Jag lider av outhärdlig smärta, värk, illamående, klåda osv.

12. DEPRESSION

- 1 () Jag känner mig inte alls sorgsen, nedstämd eller deprimerad.
- 2 () Jag känner mig lite sorgsen, nedstämd eller deprimerad.
- 3 () Jag känner mig betydligt sorgsen, nedstämd eller deprimerad.
- 4 () Jag känner mig mycket sorgsen, nedstämd eller deprimerad.
- 5 () Jag känner mig ytterst sorgsen, nedstämd eller deprimerad.

13. ÅNGEST

- 1 () Jag känner mig inte alls ångestfylld, spänd eller nervös.
- 2 () Jag känner mig en aning ångestfylld, spänd eller nervös.
- 3 () Jag känner mig betydligt ångestfylld, spänd eller nervös.
- 4 () Jag känner mig mycket ångestfylld, spänd eller nervös.
- 5 () Jag känner mig ytterst ångestfylld, spänd eller nervös.

14. LIVSKRAFT

- 1 () Jag känner mig frisk och livskraftig.
- 2 () Jag känner mig en aning utmattad, trött eller kraftlös.
- 3 () Jag känner mig betydligt utmattad, trött eller kraftlös.
- 4 () Jag känner mig mycket utmattad, trött eller kraftlös, nästan "slutkörd".
- 5 () Jag känner mig ytterst utmattad, trött eller kraftlös, totalt "slutkörd".

15. SEXUALLIV

- 1 () Mitt hälsotillstånd inverkar inte på något sätt på mitt sexualliv.
- 2 () Mitt hälsotillstånd försvårar en aning mitt sexualliv.
- 3 () Mitt hälsotillstånd försvårar betydligt mitt sexualliv.
- 4 () Mitt hälsotillstånd gör mitt sexualliv nästan omöjligt.
- 5 () Mitt hälsotillstånd gör mitt sexualliv omöjligt.

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