Aspects on Revascularization for Coronary Artery Disease

-From a Patient, Health Care Provider and Societal Perspective

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Cover illustration: Joel Grip

"Now this is not the end. It is not even the beginning of the end. But it is perhaps, the end of the beginning."

Sir Winston Churchill (1874-1965), Speech in November 1942

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ABSTRACT

Background: Balloon dilatation with related techniques (PCI) is well established for treatment of angina pectoris. New techniques, that may increase costs, have been developed with the aim of reducing the risk of recurrent stenosis and symptoms, restenosis. It has, however, not been defined what a restenosis means to the patient or what expectations patients in general have prior to investigation and treatment of coronary artery disease.

Aims: To evaluate the effects increased usage of stents in association with PCI, what it means to the patient to have a restenosis and to collect patients´ expectations, perceptions and attitudes in connection to investigation for suspect coronary artery disease.

Results: Increased use of stents in association with PCI resulted in fewer new revascularizations without influencing subsequent mortality or risk for acute myocardial infarction. The initial in-hospital costs increased but were unchanged in the long term, as were sick leaves. The patients´ perception of restenosis was dominated by the experience of "living with uncertainty". With a newly developed questionnaire patients´ expectations, perceptions and attitudes prior to and after a planned coronary angiography were collected and compared with quality of life measured with established instruments. The majority of patients had high expectations before the health care process and a positive attitude to treatment, life style changes and to be involved in the health care process. The expectations were, however, six months later fulfilled to a lower degree. Those who had their expectations fulfilled had higher quality of life and improvement in quality of life than those who did not have their expectations fulfilled.

Conclusions: Increased use of stent implantations in association with PCI reduced the need for new revascularizations but had no effects on serious cardiac events, costs or sick leaves. To suffer from a restenosis is associated with a strong experience of uncertainty that affect different aspects of daily life. Fulfillments of expectations are associated with improvement in quality of life why questions regarding fulfillment of expectations may be used as meaningful patient reported outcome measures (PROMs).

SAMMANFATTNING PÅ SVENSKA

Bakgrund: Ballongvidgning med närliggande tekniker (PCI), är etablerad behandling för kärlkramp i bröstet. Nya tekniker, vilken kan vara starkt kostnadsdrivande, har utvecklats för att minska risken för återkommande kranskärlsförträngning och symtom, restenos. Det har emellertid inte klarlagts vad en restenos betyder för patienten eller vilka förväntningar patienter i allmänhet har inför utredning och behandling av kranskärlssjukdom.

Syften: Att utvärdera effekterna ökad användning av stent i samband med PCI, vad det betyder för patienten att få en restenos och att försöka fånga patienters förväntningar, uppfattningar och i samband med utredning för misstänkt kranskärlssjukdom.

Resultat: Ökad användning av stent i samband med PCI ledde till färre nya revaskulariseringar men påverkade inte risken för efterföljande död eller hjärtinfarkt. De initiala vårdkostnaderna ökade men var på lång sikt oförändrade, liksom sjukskrivningar. Patienternas upplevelse av restenos dominerades av upplevelsen av att "leva med osäkerhet" Med ett nyutvecklat frågeformulär efterfrågades patienters förväntningar, uppfattningar och attityder inför och efter en planerad kranskärlsröntgen och jämfördes med livskvalitet mätt med etablerade livskvalitetsformulär. Majoriteten av patienterna hade höga förväntningar inför vårdprocessen, en positiv attityd till behandling och livsstilsförändringar samt av att vara delaktiga i vårdprocessen. Förväntningarna var sex månader senare inte uppfyllda i lika hög grad. De som fick sina förväntningar uppfyllda hade högre livskvalitet och förbättring av livskvalitet än de som inte hade fått sina förväntningar uppfyllda.

Slutsatser: Ökning av andel stentimplantationer i samband med PCI minskar behovet av nya revaskulariseringar men inte risken för allvarliga hjärthändelser, kostnader eller sjukskrivningar. Att drabbas av restenos är kopplat till en stark upplevelse av osäkerhet som påverkar olika dimensioner av dagligt liv. Uppfyllande av förväntningar är kopplat till förbättring i livskvalitet varför frågor om uppfyllande av förväntningar kan användas som meningsfulla patientrapporterade utfallsmått (PROMs).

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I.   Odell A, Gudnason T, Andersson T, Jidbratt H, Grip L. One-Year Outcome After Percutaneous Coronary Intervention for Stable and Unstable Angina Pectoris With or Without Application of General Usage of Stents in Unselected European Patient Groups Am J Cardiol 2002;90:112-118.

II.   Odell A, Landelius P, Åström-Olsson K, Grip L. The impact of general usage of stents on short-and long-term health care costs following Percutaneous coronary intervention. Cardiology 2008;109:85–92DOI:10.1159/000105547.

III.   Odell A, Hallberg L R-M, Grip L. Restenosis after Percutaneous Coronary Intrevention (PCI): Experiences from the patients ´ perspective. Eur J Cardiovasc Nurs. 2006 Jun;5(2):150-7. Epub 2005 Nov 16.

IV.   Odell A, Bång A, Andrell P, Widell C, Fryklund H, Kallryd A, Tygesen H, Grip L: Gender and Age Aspects of Patient Expectations and Health-Related Quality of Life before and after Coronary Angiography for suspected Coronary Artery Disease. (Submitted).

CONTENT

iv

ABBREVIATIONS

ACE-inhibitors	Angiotensin-Converting-Enzyme inhibitors
AMI	Acute Myocardial Infarction
BMS	Bare Metal Stent
CABG	Coronary Artery Bypass Grafting
CAD	Coronary Artery Disease
CCS-class	Canadian Cardiovascular Society´s-classification
CI	Confidence Interval
DES	Drug Eluting Stent
ExpQ	Expectation Questionnaire
ExpQb	Expectation Questionnaire baseline
ExpQf	Expectation Questionnaire follow-up
EQ-5D	Euro QoL group 5-Dimension self-report Questionnaire score
HRQoL	Health Related Quality of Life
MACE	Major Adverse Cardiac Event
MACCE	Major Adverse Cardiac and Cerebrovascular Event
MI	Myocardial Infarction
ns	not significant
NSTEMI	Non ST-Elevated Myocardial Infarction
OR	Odds Ratio
PCI	Percutaneous Coronary Intervention
QoL	Quality of Life
PROM	Patient Related Outcome Measure
RR	Risk Ratio
SAQ	Seattle Angina Questionnaire
SCD	Sudden Coronary Death
SD	Standard deviation
SEM	Standard Error of the Mean
SF-36	Short-Form 36

STEMI	ST-Eleveated Myocardial Infarction
TIA	Transistorisk Ischeamic Attack
TLR	Target Lesion Revascularization
TVR	Target Vessel Revascularization

DEFINITIONS IN SHORT

Acute myocardial infarction

The history of Acute myocardial infarction (AMI). Based on the following criteria AMI was defined as two of the following symptoms:

(1) Chest pain typical of cardiac ischemia and lasting for >30 minutes, (2) elevation in cardiac enzymes typical of AMI, (3) development of pathological Q waves according to the Minnesota code. The decision of the primary treating physician at the local hospital was trusted regarding the diagnosis of AMI (Studies I and II).

1 INTRODUCTION

1.1 Coronary artery disease

Coronary artery disease (CAD) is the most common manifestation of cardiovascular atherosclerotic disease and the dominant cause of sickness and death in the developed world [1]. It is even a growing health problem in many developing countries [1]. Despite the fact that age-related mortality by CAD has been markedly reduced during the last decennia, CAD still accounts for approximately 15% of all deaths in Sweden [2].

Arteriosclerotic disease often starts at a young age and is strongly related to life style factors such as smoking, high food-related calorie intake, and a lack of physical exercise [3 4]. The most important risk factors associated with manifest CAD are diabetes, age, male gender, an adverse lipid profile, smoking, hypertension, psychosocial factors, and abdominal obesity [3 5]. The development of CAD is by the progress of lipid filled plaque in the inner lining of the artery walls which leads to a thickening of the walls, with a reduction of the inner lumen of the artery. The result is reduced blood flow to the heart muscle, a decline in oxygen supply, and an accumulation of metabolic products, i.e. ischemia [6 7]. The consequences of this are dependent on the grade of coronary artery stenosis/stenoses and how quickly the stenosis/stenoses develop/s[6].

1.1.1 Stable angina pectoris

A gradual development of CAD means that the heart has time to adjust with the development of collaterals and adaption of metabolism. The blood flow may be sufficient at rest but when the oxygen demand is increased during

physical or psychological stress the flow may be insufficient and ischemia will develop. The typical clinical correlate is stable angina pectoris with symptoms in the form of pain, pressure or chest discomfort during physical or psychological stress and relief of symptoms during rest or after intake short-acting nitrates [6 8-10].

1.1.2 Acute coronary syndromes

A more rapid development of the lesion in the coronary artery, usually owing to a plaque rupture with acute coronary thrombosis, may result in the clinical manifestation of an acute coronary syndrome[6].

a) *Unstable angina* pectoris that is clinically characterized by the recent onset or rapid worsening of angina with prolonged or more severe or more frequent episodes of chest pain, or angina at rest[7].

b) *Non-ST-elevation* myocardial infarction *(NSTEMI)* is characterized by a clinical presentation such as unstable angina together with elevation of myocardial injury markers. With the very sensitive myocardial injury markers that are available today, it has been found that most patients with unstable angina have elevations of these markers which is why the terms unstable angina and NSTEMI are often incorporated into the condition termed *unstable coronary artery disease*[11] [12].

c) *ST-elevation myocardial infarction* (STEMI) is usually the result of a sudden thrombotic obstruction of one of the major coronary arteries and is characterized by chest pain, ST-elevation on the ECG that may be accompanied by affected general condition and hemodynamic deterioration[11 12].

d) *Sudden coronary death* (SCD) can be the first and only symptom in coronary heart disease. The cause of SCD may be severe ischemia

due to the obstruction of arteries supplying a large area of the heart or strenuous stress together with severe underlying CAD or arrhythmia which also may be caused by minor ischemia[13-15].

1.1.3 Silent ischemia

Ischemia may also develop on the basis of CAD, but without symptoms. This condition, that is accompanied with an increased risk of death and MI may, in its stable form, be detected during an exercise test and eventually followed by prophylactic revascularization [16]. Silent ischemia also occurs as part of acute coronary syndromes [17].

This thesis focuses on patients with angina pectoris. In Studies I, II and III both stable and unstable patients were included, but in Study IV only elective patients with stable disease were included.

1.2 Prevalence of angina pectoris and number of revascularizations

The prevalence of stable angina pectoris is very difficult to estimate and no recent studies have been identified. A survey at the end of the 1990´s revealed figures of approximately 2% at the ages 35-55 years, 3,5% at ages 55-64 and approximately 5-10 % at ages above 70-75 years [18 19]. In absolute numbers approximately 8000 patient underwent a coronary angiography due to stable CAD in 2012 and corresponding figures for unstable patients were approximately 15600 patients [20]. Approximately 20000 PCIs and 2700 CABGs are

performed annually in Sweden. Of the PCIs approximately 25% were elective for stable angina pectoris and 50% due to unstable CAD [20].

1.3   Diagnose of angina pectoris

1.3.1   Stable angina pectoris

The diagnosis of angina pectoris on the basis of coronary artery disease is based on medical history, physical examination, ECG, stress test, and coronary angiography. Important criteria are: typical chest pain which is shown during exertion and can decrease during rest, signs of ischemia during the stress test and coronary stenosis which can be shown on the coronary angiography[21 22]. The specificity of the diagnostic result of the coronary angiography has been increased by including the coronary flow reserve measurement[21].

1.3.2   Unstable coronary artery disease

The diagnosis is based on symptoms, ischemic signs on ECG and transient elevations of myocardial injury markers. Coronary angiography verifies the underlying coronary artery disease and guides subsequent decisions on revascularization. If angiography reveals stenosis/es that are amenable for PCI the procedure is often performed as an ad hoc-procedure. Widespread CAD or stenosis of the main stem of the left coronary artery is often referred for CABG[7].

1.4   Treatment of coronary artery disease (stable angina pectoris)

Treatment demands a multifaceted strategy which combines a change in lifestyle, pharmacological treatment, a suitable revascularization intervention, and physical exercise[21].

1.4.1 Life style changes

Pharmacological treatment and revascularizations are both effective at reducing the symptoms of angina pectoris but do not, however, cure the actual CAD. It is therefore of great importance that lifestyle changes are included in the treatment regime. The change in the patient's lifestyle includes smoking cessation (tobacco), physical exercise and dietary changes [3 23]. Exercise in cardiac rehabilitation has been shown to have a positive effect on mortality and the quality of life, including known risk factors [24]. The results of the positive effect of training on stable CAD has been shown in a randomized study comparing a combination of intensified training and PCI with ordinary training and PCI as well as a study comparing only training with only PCI [25 26].

1.4.2 Pharmacological treatment

Vasodilatation treatment with short- or long-acting *nitrates* has been well-established for a long time as either a cure or a prophylaxis for ischemic attacks. *Beta blockers* reduce heart rate and blood pressure and thereby reduce strain and oxygen demand [27 28]. Vasodilatation with a *calcium antagonist* has been tried with varying results [27]. Reduction of platelet inhibitors with *acetylsalicylic acid* has for several years been shown to be positive for the prevention of thrombosis in the coronary artery, thereby reducing the risk of sudden death or AMI (ref). In recent years *double antiplatelet therapy* with the combination of aspirin with a newer antiplatelet compound (clopidogrel, prasugrel or ticagrelor) has been standard for many patients either as secondary prophylaxis following a myocardial infarction or after treatment with PCI [11]. In the management of CAD today, *lipid lowering medication with statins* and *angiotensin-converting-enzyme inhibitors (ACE-inhibitors)* are an important part of the treatment [27 29-31].

1.4.3 Invasive treatment

An obvious consequence of the background of obstructive stenosis in the coronary arteries is the aim of restoring normal blood flow to the heart by mechanical means.

Coronary-artery-bypass-grafting (CABG)

Rene Favoloro began the pioneering work in 1968 and performed a surgical bypass of native coronary arteries using saphenous grafts [32]. Coronary artery bypass grafting (CABG) was then established during the years 1970-1980 as a successful method of relieving angina pectoris, but also of improving the prognosis and reducing the risk of serious coronary complications in patients at high risk [29].

Since the performances of the landmark studies demonstrating the superiority of CABG over conservative treatment in patients with high risk CAD medical treatment has, however, developed and been shown to significantly improve outcomes and reduce the risk of serious complications as well as the need for revascularization procedures [33-35]. As of today, there are no studies that have evaluated the value of CABG compared with modern pharmacological treatment.

Percutaneous coronary-intervention (PCI)

CABG as open heart surgery is a major intervention with a risk of complications and a need for long-term convalescence. Already in 1977, a less invasive technique using a balloon catheter in an attempt to expand the stenosis was developed[36]. The method was first termed percutaneous transluminal coronary angioplasty (PTCA) and was later changed to percutaneous coronary intervention (PCI) to be more inclusive for a variety of catheter-based methods. Balloon dilatation was then the basis for the later development of various types of percutaneous coronary interventions but remained the dominant interventional technique until the mid-1990s [37-41].

The method was associated with an acute risk of complications, such as vascular wall dissections caused by an injury from the balloon dilatation, which also provoked an acute thrombotic reaction[42]. Both of these mechanisms led to a significant number of acute closures of the vessel which either led to an acute AMI or the need for an acute CABG, or, in the worst case scenario even death[43]. Eventually it was clearly shown that a considerable recoil following balloon dilatation took place and that the trauma caused by the balloon dilatation in the vascular wall influenced the healing process which, in a significant number of treated patients, resulted in a new stenosis, i.e. restenosis, affecting approximately 30 % of treated patients[44 45].

Stents

To deal with the acute complications, antithrombotic treatment was developed, and thin scaffolding metal nets, stents, were developed to be implanted into the vascular wall with the help of a balloon catheter. The first coronary stent implantation in humans was done in 1986 by Ulrich Sigwart [46]. Stenting was shown to improve the geometric result and repaired eventual vascular dissections. It was also demonstrated that stents reduced the risk of restenosis by preventing recoil and achieving a larger intravascular lumen during intervention [44 47-49]. Even if a stent reduced the risk of recoil and suboptimal geometrical result in the treated vessel segment, it also produced a vascular wall injury that together with the implanted foreign material, i.e. a metal net, caused a vascular wall reaction that resulted in thickening of the vascular wall due to an increased non-striated proliferation inside the stent. As a consequence, restenosis continued to be a significant problem still affecting up to 20% of all treated patients [50 51].

Drug-eluting-stents

To solve the problem and further reduce the frequency of restenosis, stents were produced which were coated with a thin polymer loaded with antiproliferative drugs that could be released under a controlled and predestined period of time (drug-eluting stents DES). Drug-eluting stents were demonstrated to significantly reduce the number of restenosis to very low figures [52-54]. There was previously a concern regarding the long-term safety of drug-eluting stents as there has been a constant finding in several reports that DES, compared with bare metal stents, increases the risk of late stent thrombosis by approximately 0.5% per year and that this risk does not seem to vanish over time [55-57]. This issue seems, however, to have been resolved as recent data clearly demonstrates that modern DES with current antithrombotic prophylaxis are safe in the spectra of indications from stable.

Medical therapy compared with PCI

In the RITA 2 study patients were randomized between PCI and medical treatment. The patients initially allocated to PCI experienced less angina and improved exercise tolerance compared with the medically treated patients, but there were no differences in death or myocardial infarction[38]. In one study comparing aggressive lipid lowering therapy with angioplasty for stable CAD, it was found that the lipid lowering therapy was at least as effective as angioplasty at preventing ischemic events[39]. The COURAGE study showed that the addition of PCI to optimal drug treatment reduced the occurrence of angina during the first years following a PCI, an effect that, however, was attenuated after three years. Furthermore, the long-term survival or non-fatal MI and hospitalization for acute coronary syndrome was not decreased [37].

Results from these studies indicate that drug treatment including risk factor control and lifestyle intervention can be as good as or better than PCI, at least for the hard endpoints death or MI [39 58].

1.5 Outcomes of invasive interventions for the treatment of CAD

PCI was introduced as an alternative to CABG, primarily on stable single vessel disease, but later was considered for more complex lesions and was also used in acute coronary syndromes[59 60]. The high risk of restenosis with recurrence of symptoms created a need for new revascularisation procedures, CABG or PCI. Consequently, this outcome became an important measure to evaluate the efficacy of the treatment. With this background, the outcome of event free survival was established, and soon defined as freedom of major adverse cardiovascular events (MACE), a composite of death, myocardial infarction and new revascularization procedures [61]. In addition, it was further noticed that intravascular procedures imposed a risk, however small, of cerebrovascular complications which is why later cerebrovascular events were also included into major adverse cardiovascular and cerebrovascular events (MACCE) [62]. This outcome measure can be said to have been defined backwards, focusing more on complications to a medical procedure rather than on efficacy. Furthermore, this composite was created from a need to accumulate enough events in different studies to make statistical comparisons possible within a reasonable number of patients [63].

Since new revascularizations due to restenosis has been such a dominant outcome measure regarding different PCI techniques, it is of interest what impact any differences in this respect may have had on patient functional status, resource utilization, and costs.

1.5.1 Outcomes from a heath care and societal perspective

Clinical outcomes may serve as relevant efficacy measures, but in order to create the highest possible health care value not only for the individual patient but also for other patients and society as a whole, costs and resource

utilizations must also be accounted for [64]. Regarding PCI, new devices (stents) may show to be cost driving. Furthermore, the foreign material that is implanted create together with the vascular wall trauma a hypercoagulable state that require more intensive antithrombotic therapy, which also may increase the costs. On the other hand, if a new therapy reduces the need for repeated revascularizations this may be cost saving. In addition, any differences in patient health outcomes may also cause variation in hospital costs [65]. Thus, a complete comparison of different PCI methods must also account for costs associated with the different methods as well as any differences in medical outcome.

The patient´s functional status is also important, not only from the patient´s perspective but also from a societal perspective. Health is important for the wellbeing of individuals and society, but a healthy population is also a necessity for economic productivity and wealth as well as an important factor for economic growth [66]. Sweden spends nearly 10% of its gross domestic product on health care. An efficient chain of care with the patient as the focus will result in benefits in both costs and quality for each of the different actors, i.e. patients, health care system, and society. Thus, working capability may be a relevant measure. The functional status in different health-related quality of life instruments may provide information on the functional status of patients but this measure is difficult to use in retrospective studies. Sweden has a well-developed social security system with a health insurance system that covers most of the loss of income according to working incapability. Sick leaves may therefore be a meaningful outcome both from the societal and patient perspective.

1.6   Patients perspective on treatment

Since new revascularizations on the basis of restenosis have played such a dominant role in the evaluation of revascularization procedures with PCI, it is

important to put restenosis into perspective. The recurrence of symptoms after a PCI is of course a failure of the treatment and leads to disappointment, not only for the patient but also for the health care providers. Information is, however, largely lacking about what it means to the patient to experience a relapse of symptoms and to have to go through the health care process of investigations and a new revascularization procedure. There is, therefore, a great need to record patients´ perceptions and attitudes regarding this situation.

1.7 Caring

In order that the resulting care will be beneficial and safe, the patient´s own involvement is needed. Patient participation concerns having the opportunity to take responsibility for, and influence over, their health status, which can be so much more than just receiving information and advice about illness and treatment [67]. Caring theory is philosophically based on life-world theory that has everyday life and daily existence in focus in a scientific theoretical way [68 69]. Symptoms are subjective and, as such, should receive more attention and be awarded a higher value as they illustrate how a patient feels. They are especially important as they also show how a disease affects the lives of others [70 71]. Thus, the scientific research into caring provides impressions and testimony as to what it is like to live with various forms of illness. Expressing these things will give healthcare science the information it is striving for to develop measures based on principles other than medical, and an important health care scientific basis to understand what message a symptom is carrying [68]. When various symptoms can be understood, decisive actions can be developed that meet the needs of the individual so that the symptoms can be alleviated. It could be to relieve pain by different caring means, to reduce anxiety with the aid of music, a harmonious color scheme or a caring environment, and to have a daily existence in focus [68

72] [73]. All care must be based on science and proven practice. Most scientific studies highlight group values that, however, are difficult to generalize when designing care in order to benefit the individual patient [68]. Research methods that approach the individual patients and collect their individual experiences may therefore add value to the overall understanding of health care processes.

1.8 Qualitative research

Qualitative research methods work with a systematic collection of textual material from in-depth interviews and observations and to analyse the content and/or the meaning in these data in order to find new insights in the actual research field. From these new insights new hypotheses and theories could be formulated.

The main issue of all health – and medical research is that scientific knowledge is acquired in studies with selected representative persons/patients for a specific research area and that this knowledge can be applied to other persons/patients under similar conditions Thus, external validity of research results, i.e. if the knowledge is applicable to the actual patients on whom the data will be applied and/or practiced, is of fundamental importance for the credibility of the research results[74]. Regarding qualitative methods the aim is to gain a deeper understanding of patients´ experiences of their health/illness through in-depth interviews or other types of data that covers the studied field [74]. The findings from a qualitative study are not thought of as facts that are applicable to the population at large, but rather as descriptions, notions, models or theories applicable within a specified setting. Whether these results or the formed hypothesis can be applied in other settings has then to be investigated and validated in further studies[75]. Thus, care must be taken regarding transferability, i.e. when insight and hypothesis

formed from qualitative research is to be applied on new patients and patient groups [75].

Qualitative methods have advantages when a new perspective of a research area is needed. Examples of this could be approaching a phenomenon about which little is known or when the aim is to collect new information regarding issues that have been investigated previously but where it has been very difficult to gain certain knowledge by quantitative methods[75]. Grounded Theory (GT) is an inductive method for generating conceptual models or hypotheses for further testing rather than a method for verifying existing theories. GT has been developed within the discipline of sociology and has its roots in a theoretic framework of symbolic interactionism[76 77]. Symbolic interactionism explores how people define reality and how their beliefs are related to their actions and reality through attaching meaning to situations. GT has been developed gradually during the years, mainly in three stages, i.e. Glaser´s classical mode of GT [77], Strauss and Corbin´s reformulated version of GT [78] and Charmaz constructivist mode of GT [79]. GT aims at investigating the social processes within an area of research without being governed by hypotheses and prejudices but rather systematically exploring data until concepts and/or theory are emerging. In this way, also unexpected issues and perceptions will be acquired and included into the emerging model or theory[74 80]. From this perspective the consequences of restenosis contain psychosocial issues that affect the patient´s health condition as well as the actual and future life situation as a whole. To clarify the patient´s perspective of what it means to deal with a documented restenosis and going through a new revascularization, study III was performed using GT.

1.9   Health related quality of life

The concept of quality of life (QoL) has been discussed for more than 2000 years. The Greek philosopher Aristotle (348-322 BC) described a good life or quality of life as an activity [81 82]. According to Aristotle a person attains a quality of life when he/she is doing what he/she is best at or when he/she is able to be what they are meant to be. Today quality of life is more defined as a condition, i.e. with a subjective perception of living a good or bad life[83 84]. When defining QoL as it applies to health care, the term "health-related" is commonly used to focus on the effects of illness or treatment on QoL and to distinguish these from aspects beyond the realm of health care, such as education, income and quality of the environment[85]. Most Health related quality of life (HRQoL) definitions are based on the World Health Organization´s definition of health as not only the absence of disease or infirmity, but also an individual´s perspective on their degree of physiological, psychological and social well-being [86]. In this thesis, HRQoL is defined as a multidimensional experience, including various aspects of functioning and a subjective appraisal of symptoms and well-being [87 88].

1.10 Patient reported outcome measures

Completion of standardized questionnaires is a method of choice to enable, in a structured and systematic way, collection of information from the patients regarding their health status before and after an intervention. Measures collected in this way can be defined as PROMs [89] [90]. PROMs are not routinely used as key outcomes in major cardiovascular trials but PROM research has recently been recognized by the European Society of Cardiology (ESC) as an important target of interest in future cardiovascular trials[91 92].

1.11 Outcome of revascularization from the patient´s perspective

Since the primary goal of revascularization for stable coronary artery disease is the relief of symptoms and restored well-being there is, as is mentioned above, a great need to evaluate the health care process from the patient´s perspective. HRQoL instruments have been used and are validated for this patient population and in a review from Oxford University the available instruments were scrutinized and evaluated with the perspective of being used as PROMs [93]. The survey resulted in recommendations for the generic instruments Euro QoL Group 5-Dimension Self-Report Questionnaire score (EQ5D) and the Short-form-36 (SF-36), as well as the more disease-specific Seattle Angina Questionnaire (SAQ) The instruments mentioned try to obtain an overall estimation of a patient's well-being in terms of scores that can be compared between groups or over time [88 94-96] [91].

To further design the health care process in accordance to the patient's perceptions, needs and expectations, one has to find out what these really are. Thus, it is relevant to find out what matters most to a patient, what are their needs and what expectations do they have when entering the health care process. To meet the needs and expectations of patients the health care process must be governed by outcome measures that are meaningful to the patient i.e. PROMs [89 92]. In order to define PROMs that cover these perspectives, one has to start by asking the patient about their needs and

expectations. Hitherto, little has been known about the expectations of patients at the start of the chain of care and to what extent these expectations are fulfilled after investigations and interventions. [68 97].

2 AIMS OF THE THESIS

Paper I   To evaluate the clinical effects of the introduction of general usage of stents in PCI in unselected patient populations.

Paper II   To investigate if the introduction of general usage of stents has influenced hospital costs and sick-leaves.

Paper III   To describe experiences and perspectives in patients with recurrent symptoms after PCI and documented restenosis.

Paper IV   To evaluate patients' expectations, perceptions, and health-related quality of life before and after a planned coronary angiography for suspected coronary artery disease with a newly developed questionnaire and to compare this with well-validated health-related quality of life questionnaires.

3 PATIENTS AND METHODS

3.1 Study designs

Study I and II are retrospective longitudinal observation studies comparing two historical cohorts of patients. Study III is a qualitative study using the grounded theory method in selected patients, and Study IV is a prospective longitudinal observation study recruiting a consecutive cohort of patients.

3.2 A survey of the thesis, target area and populations

Four papers are included in this thesis.

In Study I all patients who underwent a PCI due to stable or unstable angina pectoris during the defined periods were included. The study was retrospective and all patients were included consecutively. The first cohort (Group A) was chosen as the last yearly cohort of patients treated with PCI due to stable and unstable angina (included from July 1992 to June 1993; 3.7% stent implantations) before the expansion of stent use, and the second cohort (Group B; included from July 1996 to June 1997; 64.7% stent implantations) as the first yearly cohort after a general routine of stent use was established.

Study II was comprised of a subpopulation of the above-mentioned with patients living and registered in the Gothenburg area, i.e. the catchment area of the Sahlgrenska University Hospital. A flow chart describing the inclusion and exclusion criteria in the studies is presented in Figure 1.

FLOWCHART
Study I and
study II

1992-1993
622 patients

1996-1997
867 patients

32 patients
with AMI

99 patients
with AMI

**Study
I**

Group A
590 patients

Group B
768 patients

424 patients not
from the
Gothenburg area

535 patients not
from the
Gothenburg area

**Study
II**

Group A
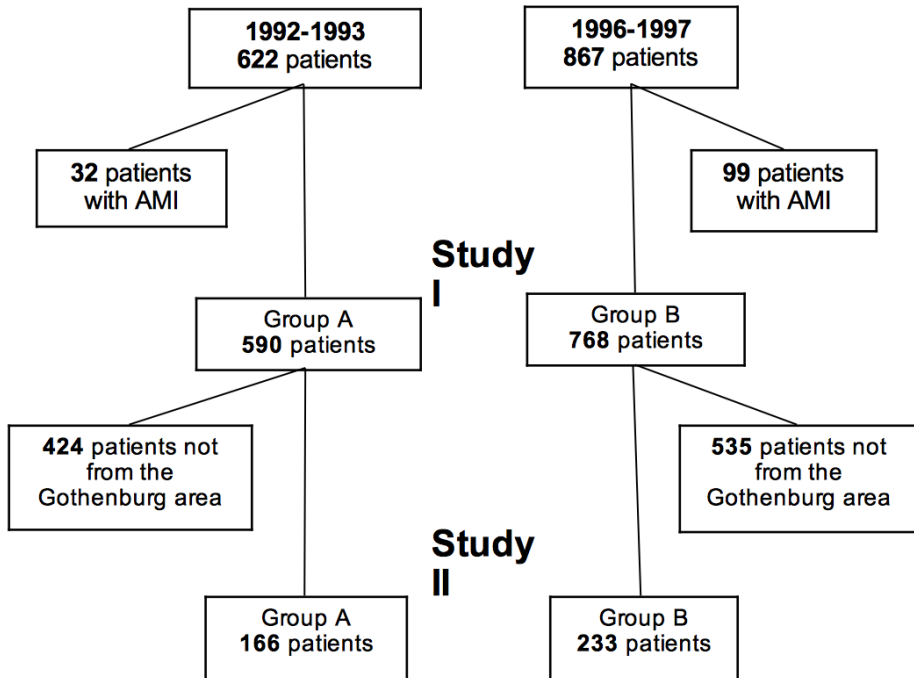**166** patients

Group B
233 patients

Figure 1. Flowchart showing the inclusion and exclusion of patients in Studies I and II.

In Study III stable patients referred for recurrent symptoms and verified restenosis after a previous PCI were included.

Study IV comprised all stable patients who were referred and planned for an elective coronary angiography for suspected CAD at all centers in the Västra Götaland region performing coronary angiography.

3.3   Ethical considerations

All studies were approved by the regional ethical review board in Gothenburg. When patients were included in Studies I and II informed consent was not compelled due to the law in the patient data act at that time (the studies were qualitative controls and retrospective observational studies and no intervention was included). Data was collected from patient medical records. In Studies III and IV, all patients who agreed to be included signed informed consent forms and were informed of their rights to end their participation at any time. The investigation conformed to the principles outlined in the Declaration of Helsinki. The fourth study was registered at www.clinicaltrials.gov (reg. no.NCT01551927).

3.4   Material samples and performance

Studies I and II

In Study 1 baseline characteristics were collected from the medical records. The results from the angiography preceding the index PCI describing the location of the CAD as well as the distribution of one-, two- and three-vessel disease were collected from the angiographic records. The result of the PCI, i.e. if it was successful, or if there were acute or sub-acute complications, was judged by the interventionist at the time of the procedure. Separate analyses were made for those who underwent PCI for the first time (de novo patients) and for those who had been previously treated with PCI, respectively.

Patients were followed-up by reviewing medical records for 12 months with respect to death, AMI, CABG and new revascularization procedures (PCI or CABG). If no data were found at the time of follow-up, a questionnaire was sent out to the patient. The letter with the questionnaire was a request for information regarding the patient's contact with the health services since the PCI procedure. We requested permission to obtain a requisition of their medical records to check if there were some data concerning the follow-up in the study. If no response was received, a reminder was sent out. In the event of no answer we again attempted to reach the patient by telephone. For each patient the occurrences of either death, AMI, CABG or new PCI were recorded. The following outcomes were accounted for in a hierarchical order: 1) occurrence of death, 2) a composite of death and AMI, 3) major adverse cardiac events comprising either death, AMI, CABG or a new PCI. Mortality was checked through the "Statistical Database on Causes of Death" with the Swedish National Board of Health and Welfare.

In Study II the follow-up period was prolonged for up to 2.5 years. All baseline data, clinical outcomes, and the follow-up were collected in the same manner as in Study I.

Study III

In Study III the baseline data that were collected comprised: sex, age, previous revascularizations and Canadian Cardiovascular Society's classifications [98]. The data were collected from the medical records after they were interviewed. The interview questions were focused on the patients' thoughts, behaviors' and feelings regarding the restenosis problem, and covered the time from first being aware of the CAD up to the time of completion of the interview. The interviews were conducted after the patients were mobilized following the coronary angiography and eventual new PCI and prior to discharge from hospital.

Study IV

In Study IV, baseline data were collected from the medical records at the time of the coronary angiography. The data from the coronary angiography and clinical outcome were collected at the time of the follow-up visit from the patients and from their medical records.

3.5   Health economy data (Study II)

Information regarding in-hospital costs was obtained from the administrative data revision office. The costs are based on the amount debited in Swedish crowns per patient treated. This was assimilated over a period of 2.5 years following the index PCI. Reasons for hospital care were classified as heart or other disease, coronary angiography, PCI or CABG. It was not possible to retrospectively retrieve reliable data on the costs for care from the outpatient clinics. All costs were reported in € (euro) and referred to the price index level of 1 January 2002. In 1993/1997, the basic index-regulated charges were € 871/912 for coronary angiography, € 2941/2971 for PCI and € 7990/9727 for CABG, respectively.

3.6   Sick leaves (Study II)

Data concerning sick leaves and retirements were obtained from The National Social Insurance Board. The risk period was 913 days (2.5 years) counted from the inclusion day until the end of the study. Only patients who were not retired due to age were included in the analysis. If, however, the patient reached the age of 65 years during the study period, the risk period was counted from the inclusion day until the day they reached the age of 65years. For standardizing, the sick leave registration was calculated from the day after the first 28 days, and all sick days were counted as whole days.

3.7 Qualitative analysis (Study III)

The aim of GT is to generate a model or a theory, i.e. a set of explanatory concepts that explains the collected data. In GT the core category is the central focus of the research topic and the emerging model or theory explains the data collected from the interviews. Related to the core category are categories that arise from the data and give information about the connotation of restenosis and how the patients are coping with the situation. The basic principle of GT is continuous sampling, analysis, comparisons, theoretical sensitivity and saturation [99]. Thus, content of this theory develops and is continuously adapted through new information and interactions between different narratives. An important point is that data collection and open coding occur simultaneously, which means that data collection and data analysis are continuous and ongoing. Study III was performed applying GT due to the systematic methodology involving the discovery of theory through the analysis of data [77-80].

Analysis of the interview data
Analysis and collection of data took place in a simultaneous process and continued until saturation of information was reached, i.e. nothing new appeared in the data. An open question was used at the beginning of the interview;-*Could you tell what you have experienced since the first time that you experienced problems from the heart?* After the first interview and analysis of this, the process continued with the second interview and it´s analysis until saturation was reached. In GT, saturation means that new data does not add new information, which is a sign to end the data collection. In the analysis process in the later data, the experiences from earlier interviews were used in an interactive way in the later data to shed more light on upcoming issues.

The first interview was transcribed immediately following the interview, followed by an analysis of the entire text. The data were read twice and from the data collected in this study the key points were marked and written in the margin of the transcripts, and recurrent words or sentences were underlined (i.e. open coding). Data from the open coding were compared with one another to find similarities and differences (i.e. substantive coding). These substantive codes were placed in preliminary categories (i.e. axial coding), and read several times and placed and replaced until the final conceptual model was formed. In the final step (selective coding) the categories were critically reviewed and, if necessary, revised to improve the reliability of the analysis. From these categories a core category was identified and proved to relate to all four categories. All these analysis steps were done with the involvement of a supervisor who also, scrutinized all data. The analyses were then compared and the codes, categories and core category were reached in consensus between the two researchers.

3.8   HRQoL (Study IV)

Short-Form (SF-36) is a generic questionnaire on health status that is well recognized, and has been validated with high reliability [100-102]. It consists of 36 questions, grouped into eight subscales; physical function, social function, role limitation due to emotional problems, mental health, energy/vitality, bodily pain and general health. A score from 0-100 can be obtained in each domain and a higher score indicates higher HRQoL.

The *Seattle Angina Questionnaire* (SAQ) is a disease-specific HRQoL questionnaire specifically used to assess the functional status of patients with angina pectoris [95 103]. The form consists of 19 items divided into five dimensions, physical limitations (how daily activities are limited by the symptoms of CAD), angina stability (assessing variations in angina during

the most exhausting activities, angina frequency (the frequency of angina episodes and consumption of short-acting nitrates), satisfaction of treatment and disease perception (assessing the burden of CAD in patients' quality of life). The results are in range from 0-100 and a higher score indicates higher HRQoL.

Expectations questionnaire

ExpQ is a questionnaire developed for Study IV in an attempt to ascertain patient expectations before and after an examination and/or an intervention in individuals with suspected CAD. The questions also concern patients' perceptions as to why an angiography should be performed, what they think the results will show, their attitudes towards various treatment options, and their views on lifestyle changes and drug therapies. In some questions the patient chooses one answer option out of several "single answer alternatives". The form also includes questions with answers ordered on a 4-point Likert scale (agree entirely, agree almost entirely, agree partially and completely disagree) for the questions regarding symptoms (impact of symptoms, physical, mental symptoms and on relatives´ concerns) and expectations (if they expect to receive all necessary information for future examinations and/or treatment, if they expect to receive the treatment that their condition requires, if they expect to receive treatment in a timely manner, if they expect to be well received by the medical staff and if they expect to be able to feel safe). The ExpQf form follows-up the expectation questions from the ExpQb form to examine how the expectations have been met. We used the 4-point Likert scale and dichotomized the answers to how the patients' expectations had been fulfilled (agree entirely) and unfulfilled (agree almost entirely, agree partially and completely disagree). One question in the ExpQb and ExpQf forms concerns issues where the patients' are requested to rank six different alternatives regarding which possible result of the examination

and/or treatment is the most important. The results are given in numbers and percentages and not calculated with points or scores.

Reliability testing of expectation questionnaire

The questionnaires were produced in two steps. The first was that knowledgeable persons on the topic reviewed it and the second step was a pilot study including 15 patients. The pilot study included both that the patients filled in a questionnaire regarding user friendliness and understandability of the questions in ExpQb and the ExpQf as well as test-retest of the questionnaires. In the test-retest the patients filled in the questionnaires twice one week apart and comparisons were made by calculating percentage agreement and Kappa values (see below).

3.9   Statistical methods

 (Roman figures within brackets denote the paper in which the respective method was used).

Continuous variables

Continuous variables are presented as means, standard deviations (SD) and standard error of the mean (SEM). Student's t-test was used for the statistical evaluation of differences between groups (I, II, IV). For comparisons between groups over time regarding sick leaves (II) and HRQoL (IV), the Mann-Whitney U test was used (II). The Wilcoxon signed-rank test was used for comparisons within groups over time (e.g. HRQoL) (IV)[104 105].

Categorical variables

Categorical variables are presented with numbers and percentages. Fisher´s exact test was used for the statistical evaluation of differences between groups (I, II, IV). For comparisons between groups regarding occurrences over time of death, AMI, new revascularizations and the composite of these outcomes, the Kaplan Meier survival analysis was used (I, II). For data with

more than two alternatives, the chi-square test was used (IV) for non-ordered data and the Mantel-Haenszel chi-square test for ordered data (IV). The Sign test was used for comparisons over time regarding ordered categorical variables (Likert scale) (IV).

Correlations

In study I primary comparisons were made between the entire groups A and B. In addition, separate analyses were made in the subgroups of those patients where the index PCI was performed for the first time (de novo) and of patients who had previously undergone a PCI.

Event rates during follow-up were estimated using the Kaplan-Meier method and the log rank test was used for corresponding comparisons between groups A and B. Hazard ratios and corresponding confidence intervals were calculated using Cox proportional hazards model, both for univariate comparisons between groups A and B and for the three baseline characteristics unstable angina pectoris, multivessel PCI and systemic hypertension, when adjusted for group belonging.

To account for impact on costs from differences in the baseline characteristics, a multivariate analysis was done using the stratum-adjusted Kruskal-Wallis test, first adjusting the outcome with regard to costs for single baseline characteristics and then including two, three and four variables at a time in the analysis (II).

For the impact of baseline characteristics on the fulfillment of expectations, a logistic regression model was used and the results are presented as odds ratio (OR) with 95% confidence intervals (IV).

Spearman's rank correlation test was used to compare the correlation of HRQoL in relation to the four different answer alternatives in the expectations fulfillment question (IV).

Calculations were performed using SPSS 11.0 and 21.0 and SAS 8.0 and 9.3.

All tests are two-sided and p-values below 0.05 were considered statistically significant.

Test-retest of the ExpQb and the ExpQf

The answers of the test and retest were compared between the two times to evaluate if they were consistent regarding percentage agreement, i.e. in how many of the answers that there were full agreement of the answers[106]. To account for random outcomes in the two tests an agreement measurement by calculation of the Kappa value ($\varkappa$) of each question was performed [106 107]. The $\varkappa$ is an agreement measure that is adjusted for expected random distribution of answers where the value 1 represents perfect (absolute) agreement and 0 a distribution that does not differ from random distribution. $\varkappa$ -values and percentage agreements of the questions regarding expectations in ExpQb and ExpQb are given in Table 1.

4 RESULTS

4.1 Patient characteristics in the Studies I-IV

An overview of patient characteristics in the four studies included in this thesis is given in Table 2.

Table 2. Overview of patient characteristics in Studies I-IV.

	Study I		Study II		Study III	Study IV
	Group A	Group B	Group A	Group B		
	n=590	n=768	n=166	n=233	n=9	n=544
Age year (mean ± SD)	60 ±9	61±10	60±10	62±10	54.2±14	65±10
	76.9/23.1	70.3/29.7	72.3/27.7	68.7/31.3	55.6/44.4	73.0/27.0
Men/Women%	%	%	%	%	%	%
Systemic hypertension	28.0%	36.6%	21.7%	35.5%	55.6%	56.4%
Diabetes mellitus	10.2%	11.0%	10.2%	12.1%	33.3%	22.9%
MI	47.3%	51.4%	46.4%	51.7%	44.4%	25.7%
PCI	14.8%	18.5%	13.3%	21.5%	100%	30.3 %
CABG	6.8%	13.8%	4.2%	14.2%	22.2%*	14.0%
Stable angina pectoris	65.8%	66.4%	60.6%	57.9%	77.8%**	100%***
Unstable angina pectoris	34.1%	33.5%	39.0 %	42.1%	22.2%	0%

Abbreviations: CABG= coronary artery bypass grafting, MI= myocardial infarction, PCI= percutaneous coronary intervention.
 *Canadian Cardiovascular Society class II-III, **= Canadian Cardiovascular Society class IV

4.1.1 Clinical outcomes after PCI (Studies I and II)

The development over time of the composite of death, myocardial infarction, and new revascularizations in Study 1 is presented in Figure 2. Thus, this composite occurred more often among the patients in the earlier recruited cohort than in the later. Additionally, the difference seen occurred during the first 6-7 months after the procedures, after which the two curves in the Kaplan Meier analysis were parallel (Figure 2).
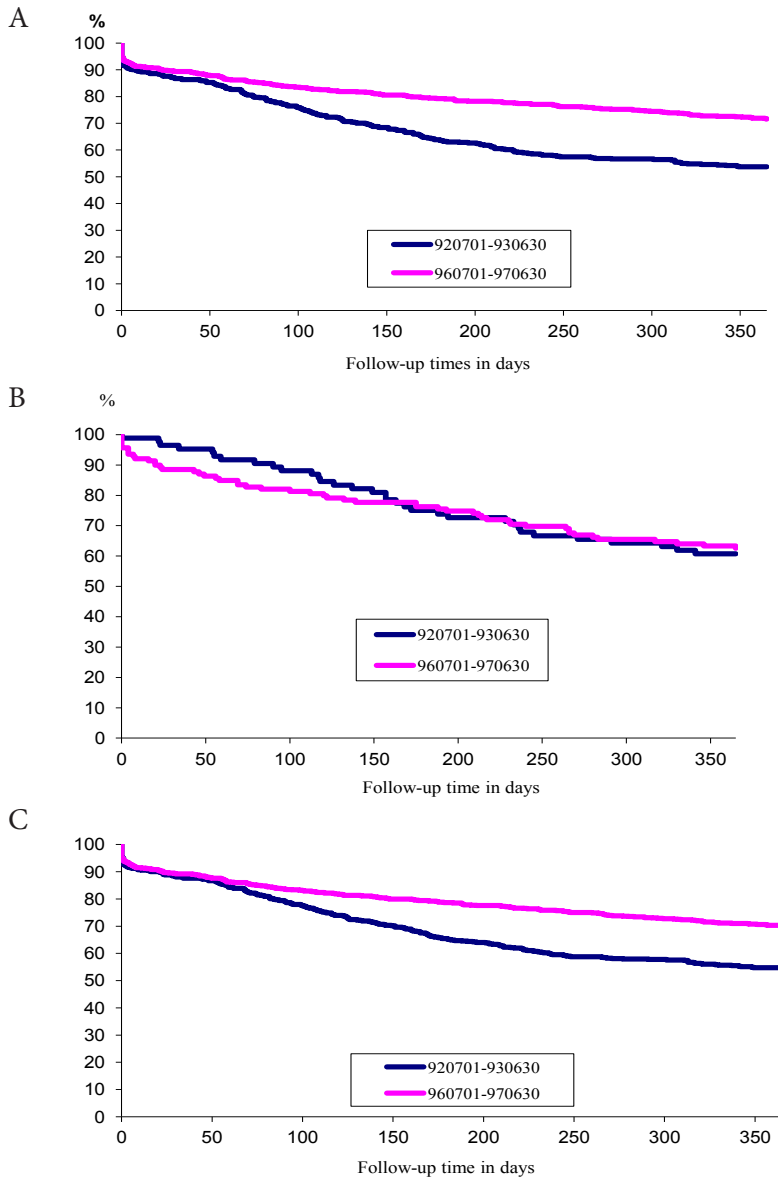
A

B

C

Figure 2 *A-C. Freedom from the composite of death, myocardial infarction, CABG or new PCI during 1 year after the index PCI procedure in groups A (blue lines) and B (pink lines).In A are given the results for all patients (p=0.0001), in B the results are given for de novo patients (i.e. patients treated with PCI for the first time; p =0.0001) and in C are given the results of patients previously treated with PCI (no significant difference).*

The development over time of the composite of death and myocardial infarction in study I is presented in Figure 3.
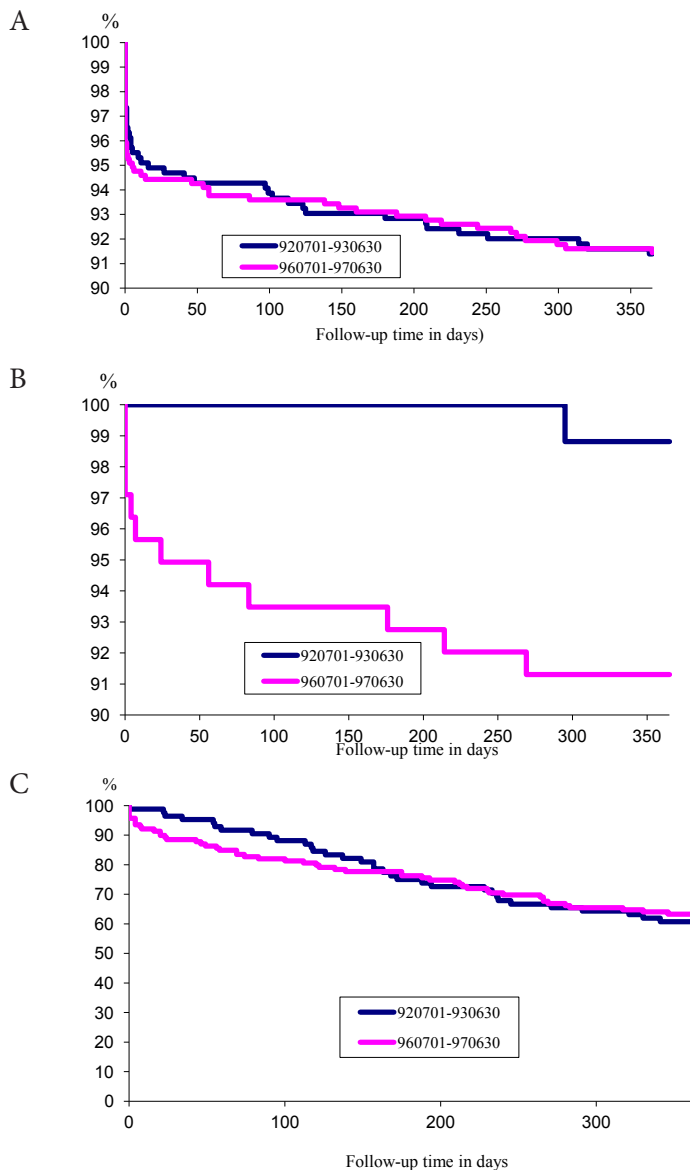
A

B

C

Figure3 *A-C. Freedom from the composite of death and myocardial infarction 1 year after the index PCI procedure in groups A (blue lines) and B (pink lines).In A are given the results for all patients (p=0.0001), in B the results are given for de novo patients (i.e. patients treated with PCI for the first time; p =0.0001) and in C are given the results of patients previously treated with PCI (There were no significant differences).*

As can be seen in Table 3, the majority of events, and the events that were responsible for the entire difference between the groups, were new revascularisations. To put Study IV into perspective, the 6-month outcome regarding mortality and incidence of AMI for this cohort of patients is also presented in Table 2.

Table 3. Results from 12-month follow-up regarding mortality, AMI, and new revascularization procedures in Study I as well as 6-month follow-up data from Study IV.

	Study I follow-up 12 month			Study IV follow-up 6 month
	Group A n=590	Group B n=768	P value	n=544
Death	2.0%	1.4%	ns	6 (1.1%)
AMI	5.0%	5.2%	ns	9 (1.7%)
Death + AMI	6.6%	6.1%	ns	15 (2.8%)
PCI + CABG	40.7%	24.6%	<0.001	262(48.2%)
PCI	31.3%	19.7%	<0.001	189(34.7%)
CABG	14.2%	6.8%	<0.001	73 (13.4%)
MACE	42.2%	27.2%	<0.001	277(50.9%)

Abbreviations: AMI=acute myocardial infarction, CABG= coronary bypass grafting, MACE= major adverse cardiac events, PCI=percutaneous coronary intervention.

Furthermore, in Study I, as is demonstrated in Table 4, restenosis (i.e. target vessel revascularizations) accounted for most of the revascularization procedures during the first year but, thereafter, approximately half of the new revascularizations were performed because of progression of the underlying CAD.

Table 4. Number of revascularizations and number of TVR per patient.

		Group A n-166	Group B n-233	P-value
Number of new revascularizations /patient				
	Treatment	0.054	0.051	ns
	12 month	0.49	0.30	0.006
	2.5 Year	0.11	0.17	ns
Number of TVR / patient				
	Treatment	0.036	0.051	ns
	12 month	0.40	0.21	0.002
	2.5 Year	0.054	0.077	ns

Abbreviations TVR- target vessel revascularization.
Treatment= time for the PCI until discharge from the hospital. 12 month= time from discharge to 12 month after the PCI, 2,5 year= time from 12 month to 2,5 years

4.1.2 Costs during and after a PCI (Study II)

When analyzing the costs associated with the index PCI and up to 2.5 years after (Figure 4) in Study II, the initial costs in Group B were higher compared with those in Group A. This difference, however, later leveled off during the first half year after the procedure, after which there was no significant difference in the costs between the two cohorts.
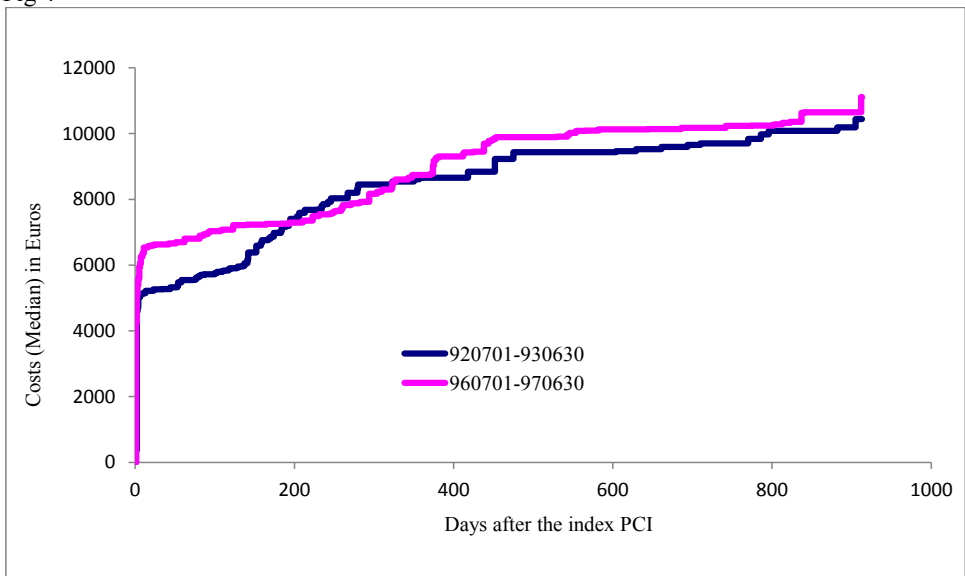
Fig 4

Figure 4. *Total cumulative median in-hospital costs given in €for the index procedure, and for the follow-up period of group A (blue line) and in group B (pink line).*

4.1.3 Sick leaves (Study II)

There were no significant differences regarding sick leaves or retirements

when compared between the two groups (Table 5).

Table 5. Number of patients and time of retirement, early retirement for health and/or other reasons and sick leave presented in number of days

	Group A n=107	Group B n=134	p-value
Patients not retired because of age during the study period	92	118	ns
Available for work, days	913	913	ns
Patients retired because of age during the study period	15	16	ns
Available for work, days	497±262	438±288	ns
Available for work (mean of all patients), days	855±174	856±	ns
Patients retired because of sickness during the study period	31	28	ns
On sick retirement during the study period (mean of all patients), days	168±297	120±281	ns
Patients on sick leave	54	67	ns
On sick leave (mean of all patients), days	130±217	115±224	ns
Proportion of days on sick leave or sick retirement of all available working days, %	33.0±44.3	29.4±40.74	ns

Abbreviation: ns= not significant

4.2 The patients´ perceptions of suffering from restenosis (Study III)

The outcome of the patients` perception of regaining angina pectoris and to have a documented restenosis after a previous PCI was of an existential nature as reflected in the core category, "living with uncertainty", of the generated conceptual model. The uncertainty was also related to the patients´ lack of knowledge and the possibility concerning their eventual responsibility for the development of the restenosis. The core category was related to four categories labeled *"fighting for access to care"*, *"moderating health threats"*, *"trying to understand"* and *"controlling relatives' anxiety"*. The related categories in the conceptual model further illustrated the patients´ uncertainty in the illness situation and were based on the interview data. Some illustrating examples from the interviews are given below:

"Fighting for access to care";

- The information given by the doctor was not compatible with the patient´s own perception of his/her illness
- To be told that "*everything is normal*" when the patients is still in pain leads to a feeling of mistrust.
- The problem for a patient to explain symptoms that are not congruent and which are not specific for angina pectoris result in a situation where the patient symptoms are not taken seriously (– ''*but according to the doctor, it was still nothing to do with the heart as the doctor said that - the ECG looked really good, therefore it must be something to do with the muscles and that I can be overwrought, and then I was told to go home!*'').

"Trying to understand";

- The patients try to find some underlying cause why just they have been afflicted.
- They attempt to find any reason for their illness (''*but I don't know if that is . . . there is surely an explanation to why. . .it has come back in precisely the same place''*).

"Moderating health threats";

- Some patients neglect the severity of CAD,
- After PCI the patients have experienced themselves as "*healthy*" again until the recurrence of pain, in which case the possibility of a new PCI will solve the problem (''*This is a part of life, it shouldn't be so remarkable . . .because it doesn't make me feel ill . . .I manage to walk and do the things I want to do except just when it becomes tight").*

"Controlling relatives´ anxiety";

- This feeling concerns the patients´ social life and how they try to moderate anxiety and worries of their relatives (– ''*My husband and my mother – they were the ones that were nervous and cried, but I knew what I would be going through''*).

To conclude, the conceptual model with a core category and four related categories concerned how patients having gone through a restenosis having to live with uncertainty for future health and not knowing if they would receive the care that they require. They also expressed that they did not want to be a

burden in the social interactions with family and friends. Furthermore, the patients tried to understand why they had deteriorated and what the reason could be why they in particular had a recurrence of their symptoms and stenosis. Thus, a conceptual model was generated with a core category, labeled *"living with uncertainty"*, which was related to four additional categories describing patients way of coping with the situation (Figure 5).
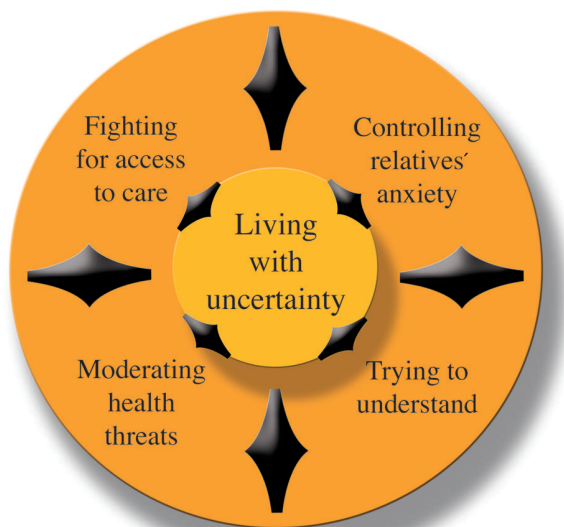

Figure 5. The conceptual model based on data from 9 patients with restenosis.
The core category, Living with uncertainty, emanates from the patients´
experiences of the arisen situation. The core category is related to four additional
categories, describing the patients´ way of coping with the situation.

4.3 Perceptions, attitudes and experiences of investigations and treatments in patients undergoing coronary angiography for suspected stable coronary artery disease (Study IV)

The patients´ perceptions regarding the reasons why coronary angiography was to be performed in Study IV are given in Table 6. More of the older than the younger patients perceived that the investigation was going to be performed to find out what was causing their condition (53.7% vs. 37.0%; p=<0.001). Furthermore, more older than younger patients (40.8% vs. 27.3% p=<0.001), and more men than women (37.9% vs. 26.0%; p=<0.005) had the perception that angiography was to be performed to find out if any in

Table 6. Patients' perceptions of the reasons for undergoing coronary angiography

ExpQb	What is, in your opinion, the main reason for you to undergo a coronary angiography?	n-544	
Q*		n	%
1a.	To investigate whether there are changes in my heart that could pose a risk for my future life.	85	16.0
1b.	To investigate what is causing my symptoms.	237	44.6
1c.	To investigate whether any intervention can be performed to make my symptoms disappear.	184	34.8
1d.	To investigate whether my heart is healthy enough for me to undergo other planned surgery (not on the heart).	18	3.4
1e.	I will be investigated prior to undergoing heart valve surgery	7	1.3

Abbreviations: ExpQb= Expectations questionnaire at baseline.
*= question number in baseline questionnaire

The patient-reported symptoms at baseline and follow-up and their significance are presented in Figure 6.

Figure 6. Results from the patients´ reported symptoms and the attitudes towards them at baseline and follow up.
Abbreviations: ExpQb = expectation questionnaire at baseline, ExpQf=expectation questionnaire at follow-up, Q= question number in baseline questionnaire, Q**= question number in follow-up questionnaire.*

The patients´ expectations regarding the outcome of the coronary angiography are presented in Table 7. More men than women (60.2% vs. 42.6%; P=<0.001) expressed a clear view that the angiography was a step towards a planned revascularization procedure.

Table 7. Patients´ expectations of findings on the coronary angiography

ExpQb	What do you expect the coronary angiography will show?	n=544	
Q*		n	%
3a.	That there is no narrowing of the coronary vessels.	82	15.4
3b.	That there is no narrowing of the coronary vessels, but not worse than lifestyle changes will suffice as treatment.	57	10.7
3c.	That there is narrowing of the coronary vessels, that may explain my symptoms and that the appropriate treatment will be with drugs.	86	16.2
3d.	That there is narrowing of the coronary vessels that can be appropriately treated with balloon angioplasty.	291	54.7
3e.	That there is narrowing of the coronary vessels that is suitable for treatment with bypass surgery.	11	2.1
3f.	That there is narrowing of the coronary vessels that cannot be treated with any of the above options.	5	0.9

Abbreviations: ExpQb =expectation questionnaire at baseline.
*= question number in baseline questionnaire.

4.3.1 Results from the Coronary angiography

The results from the coronary angiography demonstrated that altogether 32.4% of the patients had no significant stenosis, more often among women than among men (56.4% vs. 23.5%; p=<0.001) and more often among younger than among older patients (38.1% vs. 27.8%; p=0.014). Subsequently, more men than women (55.7% vs. 27.9%; p=<0.001) underwent a revascularization procedure during the study period while there was no difference between younger and older patients in this respect. Symptoms of angina pectoris were equal in men and women at baseline but at follow-up more women than men had angina symptoms (37.8% vs. 24.1%; p= 0.007).

4.3.2 Perceptions and expectations regarding decision making and subsequent treatment

A majority of the patients wanted to take part in decision making but 30.8% wanted the responsible cardiologist to take the decision on which treatment they would receive (Table 8). This attitude was more common among older than among younger patients (35.9% vs. 24.7%; p=0.013).

Table 8. Patients´ attitudes towards participation in the decision making process.

	If coronary angiography shows narrowing of your coronary vessels		
ExpQb	***What best describes your attitude towards the choice of treatment?***	n=544	
Q		n	%
5a.	I have a fixed opinion about which treatment I prefer.	20	3.7
5b.	I want to be informed about the treatment options available and then decide together with the responsible cardiologist which treatment I will receive.	355	65.5
5c.	I want the responsible cardiologist to decide which treatment I will receive.	167	30.8

Abbreviations: ExpQb =expectation questionnaire at baseline.
*= question number in baseline questionnaire.

4.3.3 Lifestyle changes and medical treatment

Regarding any subsequent treatment, most patients would have preferred PCI if given a choice (Table 9). There were more younger than older patients that preferred lifestyle changes (20.9% vs. 6.2% p=<0.001), and 28.8% of the patients would have liked to start with lifestyle changes and resort to another treatment later if it would become necessary (Table 10). The study shows that a majority of the patients could imagine lifelong medical treatment and just 5.1% did not want any medication at all (Table 11).

Table 9. Patients´ preferences regarding treatment options if the coronary angiography demonstrated significant stenosis

ExpQb	*Which of the following treatment options would you then prefer?*	n=544	
Q*		n	%
6a.	I would prefer lifestyle changes	69	12.9
6b.	I would prefer only medical treatment	49	9.1
6c.	I would prefer angioplasty	407	75.9
6d.	I would prefer bypass surgery	11	21

Abbreviations: ExpQb =expectation questionnaire at baseline.
*= question number in baseline questionnaire.

Table 10. Patients´ preferences regarding the view on changing their lifestyle

ExpQb Q*	What is your view on changing your lifestyle?	n=544	
		n	%
7a.	I would start with lifestyle changes and resort to another treatment later if it becomes necessary.	155	28.8
7b.	I would prefer lifestyle changes only as a complement to other treatment	190	35.3
	I do not want to make any lifestyle changes.	27	5.0
7d.	I have already done everything possible in terms of lifestyle changes.	167	31.0

Abbreviations: ExpQb =expectation questionnaire at baseline,
*= question number in baseline questionnaire.

Table 11. Patients 'attitudes towards medical therapy

ExpQb Q*	What is your view on a lifelong medical treatment consisting of antithrombotic, lipid-lowering and cardio-protective drugs?	n=544	
		n	%
8a.	I do not want any medical treatment.	28	5.3
8b.	I can imagine being treated with drugs for a limited time (treatment duration of about one year).	159	29.9
8c.	I can imagine lifelong medical treatment.	344	64.8

Abbreviations: ExpQb =expectation questionnaire at baseline.
*= question number in baseline questionnaire

4.3.4 Expectations regarding information, treatment, being well received and to feel safe

The patients' expectations regarding information, treatment, to be well received and to feel safe as well as the outcome of these expectations at the follow-up are presented in Figure 7.
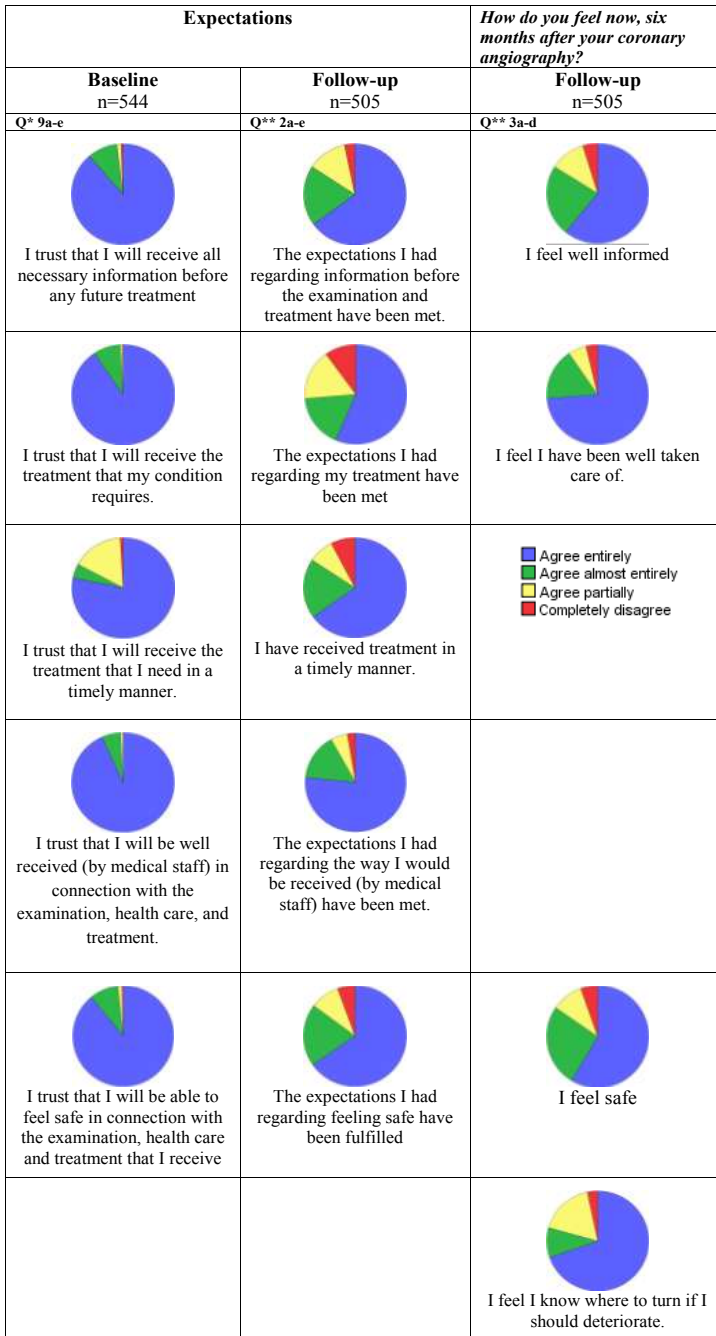
Figure 7. Patients´ expectations and the fulfillment of these expectations regarding information, treatment, being well received and feeling safe. Abbreviations: ExpQb = expectation questionnaire at baseline, ExpQf=expectation questionnaire at follow-up, Q*= question number in baseline questionnaire, Q**= question number in follow-up questionnaire.

4.3.5 Results regarding expectations and their fulfilment

Expectations, and their fulfilment, regarding recovery are given in Table 12. At baseline, there were more younger than older patients that expected to make a full recovery (63.0% vs. 51.9%; p=0.019).

Table 12. Expectations and outcome regarding recovery in baseline and follow-up.

Baseline		Follow-up		Baseline n=544		Follow-up n=505	
Do you think that your present state will be affected by the treatment you will possibly receive after coronary angiography?		**How are you feeling today compared to how you felt 6 months ago?**					
				n	%	n	%
ExpQb Q*		**ExpQf Q****					
10a.	I expect to make a full recovery / I hope to be completely fine.	5a.	I am fully restored.	306	56.9	102	20.6
10b.	I expect to be almost fully restored / I hope to improve even if I am not entirely fine.	5b.	I am almost completely restored	203	37.7	164	33.2
10c.	I expect to be only partially restored / I hope to get somewhat better.	5c.	I am partially restored.	28	5.2	115	23.3
10d.	I expect no improvement at all / I have no hopes of getting better.	5d.	I am not at all restored.	1	0.2	96	19.4

Abbreviations: ExpQb = expectation questionnaire at baseline, ExpQf=expectation questionnaire at follow-up.
*= question number in baseline questionnaire,**= question number in follow-up questionnaire

When the patients were asked to rank what was most important to them, the two alternatives that were chosen by a majority, both at baseline and follow-up, were "*wanted to be completely free of symptoms*" and *"to live a normal*

*lif*e" (Table 13). At baseline, however, 5.6% of the women vs. 12.2% (p<0.05) of the men, and 10.8% of the younger vs. 4.4% (p<0.05) of the older patients, prioritized a good understanding of their symptoms / condition. At follow-up, however, more of the women (12.2%) than the men (2.2%) (p<0.001) and more of the younger (9.0%) than the older (1.7%) (p<0.001) ranked highest the alternative to know if the symptoms / condition presented a risk for their future life and health. There were at baseline significantly more younger than older (7.7% vs. 3.2%; p<0.05) patients and more women than men who ranked highest the alternative to reduce anxiety and increase feelings of safety (5.7 vs. 1.6%; p<0.05).

Table 13. The patients ranking of what is most important to them at baseline and follow-up

Baseline/Follow-up ExpQb/ExpQf Q*/Q**		Baseline n=544		Follow-up n=505	
		n	%	n	%
11a/6a.	To be completely free of symptoms	197	41.7	174	39.5
11b/6b.	To live a normal life and be able to perform desirable activities.	183	38.8	203	46.1
11c/6c.	To have a good knowledge about my symptoms / condition.	35	7.4	15	3.4
11d/6d.	To know if the symptoms / conditions present a risk for my future life and health	22	4.7	22	5.0
11e/6e.	To obtain relief from my symptoms	10	2.1	14	3.2
11f/6f.	To reduce anxiety and increase a feeling of safety	25	5.3	12	2.7

Abbreviations: ExpQb = expectation questionnaire at baseline, ExpQf=expectation questionnaire at follow-up.
*= question number in baseline questionnaire, **= question number in follow-up questionnaire

4.3.6 Relations between fulfillments of expectations and HRQoL

Overall, there was an improvement of HRQoL from baseline to follow-up, but this improvement was significantly more pronounced among patients who experienced that their expectations to receive the treatment that their condition required were fulfilled compared with those that did not have their expectations fulfilled. (Tables 14 and 15).

Table 14. Changes in health related quality of life (HRQoL) evaluated by Seattle Angina Questionnaire (SAQ) from baseline to follow-up, regarding the fulfillment of treatment expectations

	Fulfilled expectations			Unfulfilled expectations			
	Baseline (n=272)	Follow-up (n=264)		Baseline (n=210)	Follow-up (n=201)		Between groups
	Mean (SD)	Mean (SD	p-value	Mean (SD	Mean (SD	p-value	p-value
Physical limitation	65.60 (19.1)	79.47 (19.0)	<0.001	60.1 (19.81)	65.1 (22.1)	0.003	<0.001
Angina stability	48.61 (25.0)	57.93 (20.2)	<0.001	43.9 (24.2)	53.8 (23.1)	<0.001	0.82
Angina frequencies	66.89 (26.2)	89.67 (16.4)	<0.001	61.9 (28.5)	73.6 (274	<0.001	<0.001
Treatment satisfaction	81.23 (17.2)	88.19 (15.0)	<0.001	72.7 (17.3)	69.0 (23.1)	0.4	<0.001
Quality of life	46.09 (19.2)	67.44 (19.9)	<0.001	43.1 (19.6)	54.21 (22.5)	<0.001	<0.001

Abbreviation: SD=standard deviation

Table 15. Changes in health related quality of life (HRQoL) evaluated by Short-Form 36 (SF-36) from baseline to follow-up with respect to fulfillment of treatment expectations or not

	Fulfilled expectations			Unfulfilled expectations			Between groups
	Baseline (n=272)	Follow-up (n=265)		Baseline (n=210)	Follow-up (n=202)		
	Mean (SD)	Mean (SD	p-value	Mean (SD	Mean (SD	p-value	p-value
Physical function PF	65.2 (20.9)	77.0 (19.9)	<0.001	55.8(23.9)	61.3 (25.6)	<0.001	<0.001
Role physical (RP)	42.8 (41.1)	64.2 (40.7)	<0.001	32.8 (38.4)	38.9 (40.6)	0.016	<0.001
Bodily Pain(BP)	58.7(25.1)	76.1(26.2)	<0.001	51.6 (24.1)	58.9 (26.4)	<0.001	<0.001
General health (GH)	59.0 (20.8)	68.0 (22.0)	<0.001	52.5 (18.7)	50.2 (20.5)	0.20	<0.001
Vitality (VT)	50.5 (23.7)	63.5 (24.1)	<0.001	44.2 (21.6)	48.3 (21.6)	0.03	<0.001
Social function (SF)	76.5 (23.2)	85.3 (21.7)	<0.001	67.1(26.01)	72.6 (24.1)	0.01	0.03
Role-emotional (RE)	59.4 (41.3)	75.2 (37.8)	<0.001	58.9 (43.5)	57.1 (43.2)	0.49	<0.001
Mental health (MH)	71.8 (19.4)	80.2 (18.7)	<0.001	69.2 (20.0)	69.2 (20.0)	0.21	<0.001

Abbreviation: SD= Standard deviation

Since fulfillment or not was a dichotomous variable derived from a question with a four graded answer using a Likert scale, the data was further analyzed with all the four alternatives demonstrating the same pattern (Tables 16 and 17). It was also evident, however, that patients who had their expectations entirely fulfilled not only improved in HRQoL from baseline to follow-up but that they also had better HRQoL at baseline.

Table 16. Health related quality of life (HRQoL) evaluated by Seattle Angina Questionnaire (SAQ) at baseline and follow-up in patients grouped according to their answer to the statement at follow up that "The expectations I had regarding my treatment have been met."

		Completely disagree (n=B 48; FU 44)	Agree partially (n=B 79; FU 76)	Agree almost entirely (n=B 83; FU 81)	Agree entirely (n=B 272; FU 264)	Correlation of baseline values between the four alternatives from completely disagree to agree entirely[#]	Correlation of changes from baseline to follow-up between the four alternatives from completely disagree to agree entirely[#]
		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	P value	P value
Physical limitation	Baseline	57.1 (21.5)	55.7 (17.0)	66.01 (19.9)	65.6 (19.1)	0.0001	<0.0001
	Follow-up	55.6 (21.1)	60.6 (20.9)	74.8 (20.2)	79.5 (19.0)		
	Change	-0.945 (13.943)	4.18 (15.6)*	8.25 (16.8)***	13.5 (19.2)***		
Angina stability	Baseline	41.8 (21.1)	42.3 (27.4)	46.6 (22.4)	48.6 (25.1)	0.019	0.85
	Follow-up	43.5 (21.4)	54.2 (24.8)	59.2 (20.6)	57.9 (20.2)		
	Change	2.78 (25.7)	12.2 (32.8)**	12.0 (28.8)**	9.15 (30.4)***		
Angina frequency	Baseline	58.8 (26.6)	57.9 (31.0)	67.7 (26.4)	66.9 (26.2)	0.018	<0.0001
	Follow-up	63.4 (28.9)	67.1 (29.2)	85.2 (19.9)	89.7 (16.4)		
	Change	6.14 (20.4)*	10.3 (31.6)*	17.4 (23.3)***	22.9 (26.6)***		
Treatment satisfaction	Baseline	70.8 (20.7)	73.1 (15.2)	73.5 (17.2)	81.2 (17.2)	<0.0001	<0.0001
	Follow-up	53.1 (27.8)	67.5 (21.5)	78.6 (16.1)	88.2 (15.0)		
	Change	-17.8 (29.4)**	-5.55 (23.6)	4.96 (18.0)*	6.73 (18.8)***		
Quality of life	Baseline	43.1 (20.3)	38.9 (19.5)	47.0 (18.8)	46.1 (19.2)	0.027	<0.0001
	Follow-up	45.8 (20.5)	49.0 (20.0)	63.9 (21.8)	67.4 (19.9)		
	Change	3.97 (24.9)	10.4 (22.4)***	16.3 (20.0)***	21.6 (22.0)***		

Abbreviations: SD= Standard Deviation.
For comparison between baseline and follow-up Wilcoxon Signed Ranks test were used and significance set at *=p<0.05, **=p<0.01 and ***=p<0.001.
= For comparison between the four alternatives Spearmen´s rank correlation test were used for continuous variables.

Table17. Health related quality of evaluated life (HRQoL) by Short Form 36 (SF-36) at baseline and follow-up in patients grouped according to their answer to the statement at follow up that ''The expectations I had regarding my treatment have been met.

		Completely disagree (n=B 48; FU 44) Mean (SD)	Agree partially (n=B 79; FU 76) Mean (SD)	Agree almost entirely (n=B 83; FU 82) Mean (SD)	Agree entirely (n=B 272; FU 265) Mean (SD)	Correlation of baseline values between the four alternatives from completely disagree to agree entirely# P value	Correlation of changes from baseline to follow-up between the four alternatives from completely disagree to agree entirely# P value
Physical function PF	Baseline	50.1 (25.7)	51.7 (21.4)	63.0 (23.6)	65.2 (20.9)		
	Follow-up	51.4 (25.5)	56.2 (23.7)	71.5 (24.1)	77.0 (19.9)		
	Change	0.000 (10.7)	3.73 (18.2)	8.75 (19.8)***	11.8 (19.2)***	<0.0001	<0.0001
Role physical (RP)	Baseline	27.3 (35.7)	24.7 (35.2)	43.4 (40.6)	42.8 (41.1)		
	Follow-up	26.7 (37.9)	28.2 (36.3)	55.9 (40.4)	64.2 (40.7)		
	Change	0.610 (32.4)	4.51 (40.8)	11.8 (37.1)**	21.1 (47.3)***	0.001	0.0001
Bodily Pain(BP)	Baseline	45.3 (25.1)	46.5 (19.9)	60.1 (25.0)	58.7(25.1)		
	Follow-up	47.6 (27.4)	55.7 (23.3)	68.4 (25.9)	76.1(26.2)		
	Change	0.825 (20.6)	9.21 (26.2)**	8.49 (23.3)**	16.9 (28.0)***	0.0001	<0.0001
General health (GH)	Baseline	49.1 (20.0)	49.5 (18.4)	57.3 (17.5)	59.0 (20.8)		
	Follow-up	43.8 (17.5)	46.0 (19.8)	57.9 (20.5)	68.0 (22.0)		
	Change	-4.30 (13.6)	-3.65 (19.2)	0.416 (15.9)	8.70 (20.1)***	<0.0001	<0.0001
Vitality (VT)	Baseline	37.7 (23.2)	41.2 (18.1)	50.8 (22.2)	50.5 (23.7)		
	Follow-up	41.6 (21.3)	43.7 (19.3)	56.5 (21.5)	63.5 (24.1)		
	Change	1.46 (20.3)	2.91 (19.8)	5.78 (17.4)**	12.8 (23.9)***	0.0003	<0.0001
Social function (SF)	Baseline	65.0 (29.7)	64.7 (26.2)	72.5 (23.3)	76.5 (23.2)		
	Follow-up	72.7 (26.3)	67.9 (25.3)	77.0 (20.8)	85.3 (21.7)		
	Change	5.95 (22.5)	1.86 (26.1)	4.81 (20.1)	8.78 (24.4)***	0.0001	0.041
Role-emotional (RE)	Baseline	56.5 (45.0)	54.7 (42.1)	64.1 (43.9)	59.4 (41.3)		
	Follow-up	53.6 (45.8)	47.2 (43.7)	68.3 (38.8)	75.2 (37.8)		
	Change	-2.96 (44.9)	-4.84 (53.8)	5.64 (42.7)	16.1 (47.2)***	0.70	0.0001
Mental health (MH)	Baseline	64.2 (23.7)	65.2 (19.6)	70.1 (18.0)	71.8 (19.4)		
	Follow-up	69.9 (22.6)	66.4 (19.6)	71.5 (18.8)	80.2 (18.7)		
	Change	2.44 (16.8)	1.18 (17.0)	1.28 (15.8)	8.19 (18.3)***	0.004	<0.0001

Abbreviarions: SD= Standard Deviation.

For comparison between baseline and follow-up Wilcoxon Signed Ranks test were used and significance set at *=p<0.05, **=p<0.01 and ***=p<0.001

= For comparison between the four alternatives Spearmen´s rank correlation test were used for continuous variables.

5 DISCUSSION

The background of the present thesis is the development of revascularizations with PCI and issues, concerns and questions that have been raised during this development. In particular, the rapid adoption of the use of stents during the mid-1990´s raised questions regarding efficacy, safety and cost effectiveness. Studies I and II were not designed to compare the two methods of balloon dilatation and stenting, respectively, but rather to monitor the therapeutic shift of PCI techniques and the introduction of a new technique in routine praxis. The results of these studies raised the question concerning the outcome measures which are relevant to monitor the revascularization process from the patient's perspective. Thus, from the health care perspective, results from a great number of studies covering the development of PCI have focused on restenosis and the subsequent need for new revascularizations. The importance of this issue has, however, to a minor extent not been the subject of discussion or deeper analysis, from neither the health care perspective nor even less from the patient's perspective.

5.1 Restenosis

A restenosis can mean that angina symptoms reoccur after a period of relief following the PCI. Not all restenoses are, however symptomatic, and there are considerable differences in defining needs for new revascularization whether a routine checkup angiography has been performed, as in many previous studies in the field, or not [41 44 48]. An important question is whether a restenosis imposes a risk to the patient. Restenosis has in many reviews been considered as a rather benign, albeit cumbersome, phenomenon [108]. Others argue that many restenoses are manifested as acute coronary syndromes with thrombotic complications [109]. The notion of restenosis as

a benign manifestation is, however, supported by the observation that the reductions seen regarding restenosis rate during the development of PCI have not been accompanied by any change in the rate of acute myocardial infarction or death.

The results of Studies I and II, covering an important period in the development of PCI, are, as has been pointed out above, well inline with other results and focus on the problem of restenosis both from the perspective of the health care system and partly from the societal perspective. The fact that the changes in rates of new revascularizations were not accompanied by changes in either death, AMI, costs or sick leaves raised the obvious question of what restenosis actually means to the patient. This question was addressed in Study III where patients with recurrent symptoms after a PCI and a documented restenosis were interviewed. The finding that more existential issues such as uncertainty were focused upon rather than angina and physical incapability fits in well with the results of a few studies by others [97 110 111]. With this in mind, the challenge may be to design the chain of care to be appropriate for these concerns, and that other measures than new revascularizations may be more important. Such measures may include providing adequate information to give a realistic view of the risks and benefits of the different treatment options. Thus, the findings challenge the current practice of performing a coronary angiography immediately followed by a new PCI ad hoc.

5.2   Cost effectiveness (Study II)

The above-described development of medical methods is associated with changes in resource utilizations and costs. Regarding the specific development of PCI, devices and pharmacological treatments have been

driving costs while reduced needs for new revascularizations are potentially saving costs[112 113].

Actual costs are, however, difficult to account for unless there is very detailed information on resource utilizations in different parts of the actual health care process. In a publically financed health care system that is governed by budget and the diagnose related group (DRG) system charges are more or less defined in order to cover actual costs to reach a neutral economic result for the health care provider. This is why it may be reasonable to use charges as proxies for costs, as was done in Study II. It is, however, important to bear in mind that charges may bear little resemblance to economic costs, and the use of charges as proxies for economic costs may lead researchers to draw unwarranted conclusions about economic efficiency [114]. Costs and charges are used interchangeably in studies which is why there may be serious problems in evaluating the results from an economic point of view [114].

Another issue is how to account for costs in comparisons with possible gains in medical results. Ideally and preferably used, is a cost benefit model that includes both the costs and the results of a certain measure, usually survival and some measure of well-being, i.e. quality of life. The last parameter is usually evaluated by some instrument for measuring HRQoL, commonly EQ5D (see below). The result of such an analysis may, therefore, be presented as cost per quality adjusted life years saved (QALYS). In the retrospective Study II comparing two historical cohorts, HRQoL was not assessed. A cost effective analysis was therefore applied, using hospital charges as proxies for costs, and compared the costs with the medical outcome in terms of MACE.

Finally, in a cost-income analysis both costs and consequences are expressed and evaluated in monetary terms, e.g. even the health effects are evaluated in

these terms [115]. It can be said that Study II containing such an analysis as sick leaves can be regarded as societal costs for a certain disease. Sick leaves can, however, from a patient perspective be regarded as signs of capability and, in a certain manner, well-being. As such, this parameter is a part of the cost-effectiveness or cost-benefit analysis[115].

Thus the results of Study II demonstrated that a number of new revascularizations could be saved and that from a cost effectiveness point of view there were no increased costs associated with this gain. On the other hand, the reduced numbers of revascularization procedures were balanced by increased devise and other (pharmacological treatment and monitoring, length of hospital stay) costs which is why no savings were made here either. Furthermore, the results regarding sick leaves and costs were neutral, i.e. there were no differences regarding hospital costs on the one hand and the societal costs on the other.

There are very few data from the randomized trials comparing stenting with plain balloon dilatation. Results from the STRESS study revealed higher one year costs after stenting compared with plain balloon dilatation, results supported by a non-randomized study during the same period [112 116]. Others have demonstrated neutral effects similar to those in study II [113].

Since these studies were performed there has been a development in reduced prices for stents, simplified antithrombotic therapy, and, with increased experiences and skills more procedures for stable CAD are today carried out during a one-day hospital stay. These and other factors have reduced the costs associated with PCI. This is also true if the development of drug-eluting stents is taken into consideration. To conclude, with the current knowledge the development has resulted in a reduced need for new and repeated revascularizations after a PCI with only minor differences in costs between different techniques. Thus costs are not an issue regarding different PCI

techniques and other aspects must therefore guide the choice between therapeutic options.

5.3 The patient perspective (Study I-IV)

Guidelines on treatment for stable CAD from the National Institute for Health and Clinical Exellence (NICE) stress that a good communication between healthcare professionals and patients is essential and should be supported by evidence-based written information tailored to the patient's needs [21]. The first step is to explore and address issues according to the patient's needs such as self-management skills, concerns about the impact of stress, anxiety or depression about angina and advice about physical exertion including sexual activity. Secondly it is recommended to offer individuals optimal drug treatment for the initial management of stable angina. Only if this strategy fails it is recommended to consider revascularization, CABG or PCI [21 27 117].

These recommendations are based on the notion that patient involvement in decision making is essential and are supported by studies that show that patients who are involved and take an active role in decisions about their medical care tend to have better outcomes measured by clinical parameters or satisfaction [118 119]. In line with these recommendations, a majority of all patients in Study IV wanted to participate in decision making regarding their treatment, although a minority, more elderly than younger patients, wanted the cardiologist to make all the decisions. This attitude may well has changed over time since Deber et al reported in 1996 that most patients wanted the doctor to make all the decisions, while in a later study presented in 2007 a majority of the patients wanted to actively take part in the decision making process regarding their treatment [119 120].

An important way in which the patient can be responsible and contribute to improve results is by adjusting life style in a healthy direction. As has been pointed out above, life style improvements including eating healthy food, exercise and smoking cessation are important factors and must be included in the treatment of the patients [3] In fact, life style changes on a population level have in a study been found to be a major contributor to the decreased cardiovascular mortality that has been observed in Sweden during the last decades [121]. In Study IV a positive attitude towards life style changes was found, more among younger than among older patients. It has, however, been shown that it is important to include elderly patients in cardiac rehabilitation programs after an acute coronary event, since even a short period of supervised exercise training has the potential to positively influence physical activity levels for as long as three to six years [122 123].

5.4   Qualitative analysis (Study III)

The experience of restenosis includes a subjective content and the research area includes social processes that are interactions between individuals and between individuals and the health care system and society. Thus, qualitative analysis may yield important information from the patient's perspective and help bring the research on this issue forward. Grounded theory – a theory generating qualitative methodology aimed at gaining a deeper understanding of concerns, actions and behaviours of individuals - was used in the study. Taped open interviews were conducted prior to patients´ discharge from hospital but after mobilisation following coronary angiography. The interviews focused on the patients´ thoughts, behaviours and feelings regarding the restenosis problems. Data collection and analysis of data were carried out simultaneously until saturation was met, which means that new data did not add new information. Generally, qualitative analysis intends to yield new and important information based on the patients´ perspective and

bringing the research on this issue forward. There are relatively few previous qualitative studies published in medical journals where patients´ experiences during health care processes, involving coronary revascularizations or emergency care, are reported [97 110 111]. In one of these published qualitative studies, patients who were interviewed one year after either a CABG or a PCI expressed the following narratives which emerged from the data; "*the participants were dissatisfied with the after-care*", "*the health care personnel were unable to meet and recognize the patients' problems*", "*everyday life was dominated by work*", "*the illness separated patients from their families*", "*the future was dismal and desolate*", and *"the patients lived one day at a time"* [110]. In another study using grounded theory methodology [97], patients were interviewed one month after a PCI was carried through and two categories were identified in the interview data; (1) ongoing chest pain and (2) anxiety related to fear of the unknown. A third, phenomenographic, study revealed that *"being acknowledged"*, *"struggling to become involved"* and *"having a clear space"* were three emerging categories found in interviews with patients' subjected to emergency care [111]. The results of these qualitative studies have similarities with the result of Study III,, in which *"fighting for access to care"*, *"trying to understand"*, *"moderating health threats"* and *"controlling relatives anxiety"* were identified as emerging categories. All these categories were related to a superior or a core category labelled *"living with uncertainty"* which explains what is going on in the studied field. *"Living with uncertainty"* indicates existential and social dimensions of daily living related to the heart disease and the health care process. The four strategies, *"fighting for access to care"*, *"trying to understand"*,*" "moderating health threats"* and *"controlling relatives´ anxiety"*, were used by the patients to manage their exposed situation characterized as *"living with uncertainty"*. The experience of being afflicted with a restenosis has a subjective meaning to the individuals which

was found using this qualitative research approach. According to Barney Glaser[80], the originator of grounded theory, a well constructed grounded theory will meet four central quality criteria: (1) fit with reality, (2) work and explain major variations, (3) relevance (based on its fit and work) and (4) modifiability when new data present variations[80].

5.5 Patient reported outcome measures (PROMs) (Study IV)

There are a number of PROM questionnaires and to choose the right one for a particular purpose can be challenging [90 93]. Many PROMs are designed to measure HRQoL, in a structured review of patient-reported measures used in elective procedures for coronary revascularization from the department of Public Health, University of Oxford, it was recommended to combine generic or utility measures with specific measures to assess a full range of aspects of health relevant to the particular population. Specifically, the review group recommends three instruments: the generic HRQoL instruments EQ-5D and SF-36 and the disease-specific instrument SAQ. The choices are based on volume of evaluations, good measurement and operational characteristics. These instruments have the strongest available evidence to be used to evaluate coronary revascularisation.

Of the three instruments mentioned above, SF-36 that captures both mental and physical aspects of health and SAQ, that is a disease-specific form designed to assess the functional status in patients with angina pectoris, and were chosen to be used in Study IV [88 93 95 96 103 124 125]. The results in Study IV were that HRQoL, measured with both SF36 and SAQ, improved in the entire population, A number of studies report poor HRQoL at the beginning of a coronary investigation/intervention process which is why a

positive change may either be relative and an alleviation of this condition or a true improvement due to reduced symptoms and increased wellbeing [126 127]. In Study IV there was an association between improvement in HRQoL and fulfilment of expectations (see below) which is in agreement with the results of several other studies reporting a good correlation between treatment satisfaction or degree of symptoms, and HRQoL at follow-up after cardiac catheterization or revascularization [128] [126 129 130]. There are also studies that have evaluated HRQoL after CABG or PCI [131 132]. The results have shown increased HRQoL after both procedures but being more pronounced after CABG than after PCI. Relief of angina has also been demonstrated to be superior after CABG compared with PCI [132-134].

5.6 Measuring Perceptions, notions, attitudes and Expectations (Study III and IV)

The results of Study III raised questions regarding patients' needs, perceptions and, not least, expectations at the beginning of the health care process and to what extent these were met by the end of the process. Expectations have been evaluated in previous studies using qualitative methods in the actual area covering issues such as understanding what the disease means, relative information about it and treatment perceptions [97 110 125 135 136]. Quantitative studies have evaluated treatment expectations prior to, and satisfaction of treatment after hip and knee replacements [137 138] [139]. Regarding CAD and revascularization with CABG and efficacy expectations a scaling instrument has been produced but not widely used

[140] [93]. For investigations aimed at decisions regarding revascularizations, no established forms for measuring expectations before investigations or interventions and satisfaction or fulfillment of expectations have been identified.

Overall, the results of study IV revealed that at baseline there were high expectations of receiving information, treatment that was required in time, being well received by medical staff, feeling safe and or achieving a full recovery and freedom from symptoms. This is in line with other studies that have measured expectations in patients in the same kind of health care systems [137-139]. At follow-up, however, the fulfilments of these expectations were lower and almost half of the patients did not fully agree whit having had their expectations regarding treatment fulfilled. Furthermore, about one quarter of the patients still reported symptoms that greatly affected and limited them and limited their living an active life. Additionally, a considerable proportion of the patients claimed to not be fully recovered. Even if those who did not have their expectations fulfilled had more angina pectoris at follow-up, there was a considerable overlap between the fulfilment of expectations and symptoms. Furthermore, a logistic analysis showed that patients with previous CABG and diabetes had less fulfilment of expectations, however, regarding revascularizations in the actual health care process there was only a non-significant correlation between fulfilment of expectations and performed revascularizations. This means that neither freedom from symptoms nor a performed revascularization procedure predicted full treatment satisfaction or the fulfilment of expectations. Thus, the needs and expectations of patients suffering from CAD may be rather more complex and further studies and analyses have to be carried out in order to adjust the health care process to meet these needs.

In order to collect the information regarding patients' perceptions, notions, attitudes and expectations before the health care chain with a planned coronary angiography and to follow-up treatment satisfaction and fulfillment of expectations a new questionnaire was developed. Reliability tests revealed that most of the questions were found to be adequate.

If an instrument is to be widely used validity evaluation is important [106 107]. In Study IV the validity of the ExpQ forms was tested by comparing the compliance of the results with those of the HRQoL included in the study. Thus, we found that fulfilment of expectations was related to most dimensions of HRQoL measured by both SF-36 and SAQ. This was the case for both baseline HRQoL and HRQoL at follow-up.

5.7   Gender and age perspectives (Study IV)

One of the main aims of Study IV was to find out if there were variations between different ages or between men and women regarding perceptions and expectations. Other studies that have evaluated HRQoL after a health care process including cardiac catheterization with or without revascularization report poorer HRQoL among women than among men, a finding that was confirmed in Study IV [101 141]. Furthermore, in Study IV, there were indeed a few differences in the results between men and women as well as between younger and older patients. Thus, among women and younger patients the needs to understand and to have knowledge concerning the disease including what is causing the symptoms were more often pronounced than among men and older patients. Women also expressed more often a need to cope with worries about the future and to reduce anxiety. These aspects have similar existential and conceptual content as was found in Study III which indicates a link between the qualitative study and the quantitative data.

A majority of the women prior to the angiography expected it to demonstrate either no significant stenosis or a degree of CAD that would not necessitate a revascularization procedure, whilst a majority of the men expected that the result would lead to a revascularization procedure (PCI). This is interesting since it complies well with the actual findings that woman, as well as younger patients, less often had significant stenosis. This result is in concert with other studies that have also demonstrated that many patients undergoing coronary angiography do not have any significant stenoses, and that this is more common among women than among men [125 142]. Subsequently, in Study IV, women less often than men underwent revascularization while there was no difference in this respect between younger and older patients. At baseline the symptoms of angina were equal in men and women but there were more women compared with men that reported angina at follow-up.

5.8 Limitations

In Studies I and II were found that the therapy shift to more frequent usage of stent implantations reduced the number repeated revascularizations but that there was no impact on clinical events such as death or myocardial infarction. The latter finding must, however, be interpreted with great caution. Although the patient populations were not small, the numbers of these serious cardiac events were small and the possibility of a statistical type II error must be recognized. The finding is, however, well in concert with findings by others why it is a reasonable conclusion that it reflects the true effect of the therapeutic shift [41 44 47].

The problem of sample size and the risk of a type II error is also a concern regarding the reliability testing of the Expectations

questionnaires that was carried out in only 15 patients. Furthermore, the distribution of answers in the questions with several answer alternatives was skewed. Thus few observations had a great impact on the results of the test-retest. The agreement among the subjects was, however, good with high levels of percentage agreements and kappa-values indicating at least good agreements in the test-retest procedure. Furthermore, the patients expressed approval of the questionnaires as they were. Still if the questionnaire should be used in further studies it ought to undergo extended reliability testing and validation.

The same issue of sample sizes and validity of data may also be a concern regarding the qualitative analysis using the method of Grounded Theory. A fundamental part of the method is to collect enough data to mirror all aspects of the subject that is investigated and reach a stat of saturation [99]. There will always be a risk that important information will not be given by the actual patients or skewness in the data is collected. The results of study III focus on existential aspects that to some degree were also observed in the data that were that came forward in Study IV. In general, however, patients in Study IV were more focused on symptoms and issues connected with revascularizations rather than worries and conceptual issues. The difference may be due to different patient populations or methodological and created by the different techniques of collecting data and that answers retrieved by questionnaires may be biased by the formulation of the questions.

The current thesis is focused in the treatment of patients with stable CAD, although patients with unstable angina are included in Studies I

and II. It must be kept in mind, however, that at the time when the studies were performed a rather conservative attitude towards early revascularization in patients with unstable angina was practiced. Thus there was always an attempt to stabilize the patient medically and only if this was unsuccessful, or if there were signs of severe angina, an early revascularization, PCI or CABG, was performed. Many patients with unstable angina were stabilized and referred for a more or less elective angiography. Thus, at the time of Studies I and II a majority of all patients who underwent coronary angiography and subsequent revascularization were stable and the unstable patients at the time were quite different of those that today undergo an early angiography that very often is followed by a PCI ad hoc. The results of the present thesis are, therefore, applicable mostly to patients with stable angina pectoris.

6 CONCLUSION

The introduction of general usage of stents resulted in reduced need of new revascularisations but there were no impact on the risk of death or myocardial infarction after the PCI.

The introduction of general usage of stents increased immediate health care costs that later levelled off and there were no differences in neither long term costs nor sick leaves compared to what was observed with previous treatment routines.

Patients' perceptions of illness and illness-related events, such as symptoms, diagnosis, treatment and prognosis, are considerably affected by uncertainty. This infiltrates their struggle to acquire the care needed, their endeavour to comprehend and moderate health threats, and caring for their family.

Fulfilment of expectations after coronary angiography is related to improvement in health related quality of life. To measure patients´ expectations and fulfilment of these may be a simple and meaningful patient reported outcome measure to evaluate a health care process from the patient's perspective.

7 FUTURE PERSPECTIVES

In Study IV was collected a large amount of data and Paper IV focuses on describing the questionnaire and the overall results for patients with suspected coronary artery disease. There were however, more data collected. These and the presented data warrant further analyses that have the potential to reveal interesting information.

- First, as has been pointed out, the instrument need further reliability and validity testing before it is to be used in future studies. Although some of the questions can be identified as reliable and interesting, the entire battery of questions needs to be scrutinized to find an optimal composition.

- A further analysis of the data with regard to mode of revascularization, CABG or PCI, will be of interest in order to evaluate the two revascularization methods from a patient perspective.

- Data were also collected from patients investigated for valvular disease with, in many cases, subsequent surgical valvular replacements. Data will be compared between these patients and those included in Paper IV.

- A deeper analysis of the patients that were without significant coronary stenosis will be conducted.

- Patients had the possibility to write down comments in free text in the questionnaires and it is planned to perform a content analysis of these data.

- Blood samples for analysis of NTpro BNP were drawn at baseline for all patients and for approximately half of the patients at follow-up. The samples have been analyzed and an evaluation of possible correlations of levels of NTproBNP, as a measure of strain to the heart, and clinical variables, HRQoL and fulfillments of expectations is planned.

- Finally, it would be of interest to use a modified version of the presented questionnaire to measure PROMs in future interventional studies to investigate if differences and changes in therapies will be reflected in the answers. As a part of this it would also be of interest to try to tailor health care processes with the guidance of these measures.

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