Patient-reported outcomes after on-pump and off-pump coronary artery bypass surgery

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List of papers

Paper I
Lars Mathisen, Per Snorre Lingaas, Marit Helen Andersen, Per Kristian Hol, Per Morten Fredriksen, Kjetil Sundet, Berit Rokne, Astrid Klopstad Wahl, Erik Fosse.
Change in cardiac and cognitive function, and patient-reported outcomes at one year after coronary artery bypass surgery. (Submitted)

Paper II
Preoperative cerebral ischemic lesions predict physical health status after on-pump coronary artery bypass surgery.

Paper III
Lars Mathisen, Marit Helen Andersen, Per Kristian Hol, Per Snorre Lingaas, Runar Lundblad, Kjell Arne Rein, Tor Inge Tønnessen, Bjørn Erik Mørk, Jan-Ludvig Svennevig, Astrid Klopstad Wahl, Berit Rokne Hanestad, Erik Fosse.
Patient reported outcome after randomization to on-pump versus off-pump coronary artery surgery.

Paper IV
Lars Mathisen, Marit Helen Andersen, Marijke Veenstra, Astrid Klopstad Wahl, Berit Rokne Hanestad, Erik Fosse.
Quality of life can both influence and be an outcome of general health perceptions after heart surgery.
Health and Quality of Life Outcomes 2007; 5:27.
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## Abbreviations

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<td>CABG</td>
<td>Coronary artery bypass grafting. This abbreviation designates the surgical procedure, regardless of whether an on-pump or off-pump technique is used.</td>
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<td>CCS</td>
<td>Canadian Cardiovascular Society angina classification scale.</td>
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<td>MRI</td>
<td>Magnetic resonance imaging.</td>
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<td>SF-36</td>
<td>Short Form 36 item version of the Medical Outcomes Study health status questionnaire.</td>
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<td>QOLS-N</td>
<td>Quality of Life Survey – Norwegian version.</td>
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**Introduction**

Ischemic heart disease is prevalent in the industrialized world, ranking high as a cause of death (1) as well as affecting physical and psychosocial health (2-7). For selected groups of patients with ischemic heart disease, coronary artery bypass graft surgery (CABG) aims to prolong survival, relieve symptoms (angina pectoris), improve functional status and thereby improve the quality of life (8-11). The main theme of this thesis is the secondary and patient-reported group of outcomes following CABG surgery; angina, health status and overall quality of life.

The patient volume of CABG procedures averages 3000-3500 annually in Norway or around 60% of all heart surgeries performed (12). Under general anesthesia, a leg vein or an artery, most often the internal thoracic (mammarian) artery, is used to conduct blood past the narrow coronary arteries and thereby restore blood flow to the heart muscle. There is a potential for adverse cerebral events with neurological impairment, ranging from stroke through transient confusion to more subtle cognitive dysfunction with varying duration and psychosocial significance (13-16). Surgery is followed by up to 24 hours of intensive care. Discharge from the hospital setting is usually scheduled within one week after surgery.

Outcomes evaluation calls for two distinctly different sets of data. Survival data are objective, straightforward to define, and an extensive literature exists to evaluate the efficacy of CABG surgery in relation to the primary aim: prevention of sudden death and early mortality (17-19). The secondary aims refer to subjective experiences, or patient-reported outcomes. The patients’ own assessment of their symptoms, health status and overall quality of life reflects the experience of illness as well as the impact of CABG surgery (20-23). Previous studies largely agree that at the group level, patient-reported outcomes improve after CABG with a transient decline during the recovery period (24;25). However, there is considerable variation at the individual level (26;27), which inspires a field of research aiming to improve on patient selection and patient management. It is known that the coronary angiogram, used to evaluate the extent of ischemic heart disease, is not an accurate predictor of the subjective experience of disease: individuals may be asymptomatic, yet have severe coronary stenosis carrying a high risk of sudden death, or they may have severe angina inconsistent with the extent of coronary artery stenosis (8). Moreover, symptomatic improvement after CABG appears to benefit broader groups than
those improving longevity (8), which means that extrapolation of survival data alone is insufficient to predict patient-reported outcomes.

The individual experience of CABG surgery may differ with respect to benefits as well as possible adverse effects. Conventionally, in order to immobilize the surgical field and to protect the heart, a heart-lung machine is used to oxygenate and transport blood during cardioplegic arrest. It has been suggested that ‘beating heart’ coronary artery bypass surgery (28-32) may be performed with a lower incidence of neurological adverse effects believed to be associated with extracorporeal circulation (33-36). The answer to which procedure appears superior may be determined through randomized clinical trials (37). In this context, the experiences of patients are valuable in a broad comparison of therapies that may be equally effective regarding traditional clinical end-points, but may have different profiles regarding patient-reported outcomes (18;23;38-41).

As patient-reported outcomes become more complex and abstract, their associations to clinical variables and observed functional performance become more challenging to interpret. Research is needed to map these associations, clarify the content and boundaries of concepts, and test causal assumptions regarding the effect of CABG surgery on patient-reported outcomes. The main aim of this study was to document and interpret patient-reported outcomes, ranging from symptoms through health status to overall quality of life, after convalescence and during the first year following on- and off-pump coronary artery bypass grafting.

**Patient-reported outcomes: concepts and definitions**

CABG surgery aims to improve the quality of life (8). The term patient-reported outcomes is an umbrella term for a wide range of outcomes related to health care, including the impact of an intervention on health and quality of life, satisfaction with treatment, or utility-based preferences (23;38;42;43). The defining characteristics are the patient as a source of data (44), and the context of being a patient – that is, the requestor and/or recipient of health care (45). Patient-reported outcomes are concerned with the experience of an illness more than the disease itself (46), and provide a unique source of insight (2;21;38;47;48). Self-reported patient assessments can be collected reliably (8). There is a growing acknowledgement of the importance of patient-reported outcomes when evaluating health care interventions (8;38;49-52). The impact of an intervention such as CABG can be measured on a range of outcomes from the purely symptomatic to more complex concepts (functional capacity), to
extremely complex concepts such as quality of life (20). A central challenge is the ability to link patient-reports outcomes to clinical endpoints (21). In this thesis, theoretical modeling, patient-reported assessments and objective assessments are combined to investigate these links in patients undergoing CABG surgery. Patient-reported outcomes research may help to identify vulnerable as well as resilient subgroups among CABG patients, and support evidence-based patient counseling regarding the expectations of CABG surgery (53). Moreover, the patient’s own appraisal can promote patients’ involvement in decision-making at the individual (21) as well as at the group level, with the possibility of extending this influence into cost-utility analyses (43;54;55).

Symptoms – the perception of an abnormal physical, emotional or cognitive state (21) – are conceptually well-defined. The concepts health status and quality of life require a brief introduction. Overall quality of life has been described in terms of well-being, life satisfaction, and happiness (56-58). The quality of life concept represents a paradox; while people seem to have an intuitive and established understanding of the content (56), consensus is yet to be reached in the scientific community on a formal and universally accepted definition (38)p.4,(21;23;44;59;60). Thus, from a conceptual and an empirical perspective, the mechanisms and extent to which CABG impacts on the quality of life is open to modeling and evaluation.

A distinction should be made between the determinants or causal influences on quality of life, and the actual experience or perception of having a greater or lesser quality of life (58;61;62). Although overall quality of life may seem to overlap with a wide definition of health (51;63), quality of life is not restricted to the impact of health states and health care, and may represent the influence of other salient life experiences and circumstances (21;22;64). Individuals with severely impaired health may perceive their quality of life as high, or better than others with optimal functioning (65;66). The appraisal of overall quality of life may have a moderating influence on the experience of illness and treatment (21;44), suggesting a possibility of bidirectional causal relationships when modeling the impact of health status on overall quality of life.

The terms self-reported health status and health-related quality of life are used interchangeably to label a subset of patient-reported outcomes to evaluate change in or maintenance of current state of health (8;21;67). While the term health-related quality of life identifies a set of causal determinants of overall quality of life, this does not imply that the experience of overall quality of life may be divided into health- and non-health related
dimensions (58;68). It is generally agreed that a comprehensive health status assessment must cover physical, mental and social dimensions (38;67). Health status is expected to vary with disease activity and treatment, although not necessarily in a linear fashion. Clinical parameters of disease activity appear to account for a limited range of variance, with correlation coefficients in the area of 0.20 – 0.40 (21).

**Theoretical framework**
A theoretical framework is used in this thesis to hypothesize relationships between clinical variables, observed outcomes and patient-reported outcomes, to suggest causal relationships within patient-reported outcomes, and to guide variable selection. The mechanisms and factors that influence subjective appraisals are complex and incompletely understood. Although some theoretical modeling has been attempted (21;69-71), further research is needed to empirically assess the relationships of interventions and patient-reported outcomes, advance clinical interpretation of patient-reported outcomes, and to test and refine existing theoretical models (21).

**The Wilson and Cleary Causal Pathway Model**
A causal pathway model, proposed by Wilson and Cleary in 1995, links clinical variables with patient-reported outcomes (21). The model structures different levels of outcomes along a continuum of increasing complexity, from biological/physiological parameters through patient-reported outcomes with the final endpoint being overall quality of life (Figure 1). In doing so, this model represents a transition from a broad conceptual understanding of patient-reported outcomes to operational definitions that can be integrated in research questions, variable selection and a plan for analysis. CABG surgery modifies anatomical structures with the intent of improving bio-physiological variables: corresponding objective outcomes indicators at this level are the angiogram and performance on an exercise test. Starting at the level of symptoms, the patient-reported outcomes refer to four hierarchical levels: symptom status, functional status, general health perceptions and overall quality of life. The causal paths illustrated are predominantly from left to right, although the opposite may be present, i.e. concurrent and bidirectional paths. Individual and environmental characteristics may modify outcomes at all levels.
Symptoms are physiological or pathophysiological phenomena as they are recognized and experienced by the patient. The primary disease specific indicator is the existence of angina, and the level of activity that will produce angina. Measures of function, on the other hand, are assessments of “the ability of the individual to perform particular defined tasks” (21). Thus, the perception of chest pain, regarding intensity and the trigger events, relate to the symptom level. However, when evaluating the limitations that chest pain inflicts on everyday life, focus shifts to the consequences of symptoms and the next level of outcomes labeled functional status. In this thesis, patient-reported outcomes were measured as symptoms, health status (functional status and general health perceptions), and overall quality of life.
Conceptual definitions in this thesis

Patient-reported outcome
A patient-reported outcome is “a measurement of any aspect of a patient's health status that comes directly from the patient (i.e., without the interpretation of the patient's responses by a physician or anyone else)” (20). In this thesis, patient-reported outcomes are measured as symptoms, health status and overall quality of life.

Overall quality of life
The overall quality of life is defined as “a person’s sense of well-being that stems from satisfaction or dissatisfaction with the areas of life that are important to him/her” (60).

Health status
Health status includes the patients’ perception of functioning, disability and well-being related to physical, mental and social dimensions. These dimensions consist of eight concepts: physical functioning, role limitations due to physical problems, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health (72). The terms ‘health status’ and ‘health-related quality of life’ are used interchangeably (21). Schipper asserts that health-related quality of life represents the patients’ experience of illness and treatment across bio-psycho-social domains of functioning and well-being (22).

Symptom
“A patient’s perception of an abnormal physical, emotional or cognitive state” (21).

Coronary artery bypass surgery
Pioneered in the 1950s (73;74), surgical revascularization for coronary arteriosclerosis was greatly facilitated by coronary angiography (75), and the procedure developed in the USA during the 1960s using cardiopulmonary bypass (76;77). In 1964, the Russian surgeon Vasillij Kolessov reported on the anastomosis of the internal mammary artery to the left anterior descending coronary artery without use of cardiopulmonary bypass (28). Randomized studies in the 1970s and early 1980s compared CABG surgery with pharmacological management, and survival data from these trials demonstrated the beneficial effect of surgical therapy (17;19). As one of the most studied and well
standardized surgical procedures commonly performed, the body of literature is extensive. Periodical reviews are commissioned by guideline developing institutions (8;10). In the following paragraphs, the scope of a focused literature review concerns the aims of this thesis.

**Objective outcomes**

Survival after CABG has been reported to reach 97% at 1 year and 92% at five years after surgery (78). The benefits of CABG surgery are believed to result from an increase in coronary flow reserve, or the increase in flow in response to an increase in myocardial oxygen demand, with a subsequent increase in observed exercise capacity and relief of angina. Functional performance may be measured with a graded exercise stress test protocol (79). The effect of CABG on exercise capacity appears sensitive to the completeness of revascularization (80;81). However, early CABG experience demonstrated that coronary flow may increase in myocardial segments beyond those expected to be supplied by a grafted native vessel (82), and that segmental wall contractility may improve in other areas than those supplied by grafted vessels (83). Providing that sufficient global improvement in coronary flow reserve has been achieved, the functional benefit of coronary grafts placed may outweigh variance represented by the total number of grafts.

Graft patency, visualized by coronary angiography, is established as an indicator of surgical quality. However, graft patency rates do not directly address the adequacy of grafts in providing myocardial perfusion (84). Graft patency is dependent upon a number of factors, including surgical quality (85), blood flow in the recipient area, the conduit material, and anticoagulants (86;87). Freedom of reintervention (CABG or percutaneous coronary intervention) appears to decrease slowly until five years and later after initial surgery (88).

**Adverse effects**

CABG may induce complications from the cardiovascular, pulmonary, renal, gastrointestinal, endocrine, immunological and neurological subsystems (89). In isolated, first time and elective CABG surgery, a higher perioperative risk is associated with gender, age and the presence of neurological dysfunction, extra-cardiac arteriopathy, pulmonary hypertension, or an elevated serum creatinine (90). The unadjusted operative mortality associated with CABG varies in the literature, often in the range of 1.5% to 3% (12;91-94).
Conventional CABG requires temporary cardiac arrest to allow for suturing of grafts on the non-beating heart. This has been technically possible due to intraoperative cardiopulmonary bypass and myocardial protection techniques, using a heart-lung machine to temporarily take over the functions of oxygenating and pumping arterial blood. Immobilization of the surgical field is achieved at a price: the foreign body surface of the cardiopulmonary bypass circuit induces immune system activation (95). Cannulation and aortic cross-clamping procedures may lead to the formation of gaseous or particulate emboli which may enter the cerebral circulation (96;97). Global or local hypoperfusion with ischemia during the procedure may trigger activation of the cascade systems with end-organ effects. Possible cerebral effects related to hypoperfusion, microembolization or immune activation range from stroke (98) through transient delirium to subtle neurocognitive impairment (13-16). Cognitive dysfunction has been demonstrated in 75% of patients at one week after surgery (99). Others have found postoperative cognitive dysfunction to improve over time and approach 20% at two months (100), although the incidence cited varies widely with study population and methods of investigation (101-103). A possibility of long-term implications of cognitive decline associated with CABG surgery has been suggested (102;104), although the cross-sectional data do not necessarily imply a causal association. Postoperative cognitive dysfunction has also been demonstrated at 3 months after non-cardiac surgery in up to 10% of the patients (105).

Patient-reported outcomes after CABG surgery

The intermediate outcomes of CABG, relief of angina and improvement of cardiac performance, are expected to have a positive causal effect on the quality of life (8;21). From the 1970s, the theme of quality of life enters the CABG literature using indicators such as work status, physician-determined functional classification, and ergometric test data (39;106;107). Following CABG, patients could resume or initiate new physical and social activities, taking on a “new lease of life” (108). Initially, the presence and intensity of angina was the main available indicator of quality of life. After 1980, a wider range of patient-reported outcomes appeared (109-111), although research prior to the middle of that decade did not explicitly model the assumptions underlying the selection of outcomes or the relationships between indicators. The level of modeling mirrored the level of conceptual development regarding quality of life. Qualitative studies have added to the understanding
of what ischemic heart disease, angina and CABG surgery mean to the patients (5;7;112-115), also as seen from a gendered perspective (116-118).

Previous cross-sectional and longitudinal studies of CABG surgery have described patients’ perceptions during the waiting period before surgery (119-121), in the early postoperative phase i.e. first two months (122-126), during convalescence and through the first year after CABG (109;123;127-144), and in the long term follow-up beyond 12 months (18;145-151). Overall, patients appear to improve in health status after CABG, although both improvement and decline in individual health underlies the group level results (24;27;142;152;153). Within the first year after surgery, the greatest changes in health status have been reported to occur during the first six months (154). This general pattern is also reflected in the Norwegian context; While the period of early convalescence may be challenging in terms of pain management (155) and possibly unrealistic expectations of a swift recovery (122), four studies report a benefit of CABG on health status beyond the convalescence period after surgery, at one year (135;156;157) - coinciding with physician-determined functional classification (135) - and at three years (158) after revascularization. Comparison to a reference population demonstrated similar health status also among the older respondents, while post-CABG patients were noted to report lesser bodily pain than the population norm (156;158). In one recent study, female patients reported lower health status than their male counterparts, as well as a lesser health gain after CABG (157). For preoperative patient counseling as well as to identify individuals who deviate from the expected trajectory after CABG, research is needed to understand the extent and the mechanisms of individual variation in patient-reported outcomes.

**On-pump or off-pump CABG?**

Reintroduction of ‘beating heart’ coronary artery bypass surgery (30-32), with newer mechanical stabilizers to facilitate coronary anastomoses (159), induced expectations of a less invasive procedure and the avoidance of adverse cerebral events associated with cardiopulmonary bypass. In early clinical experiences, off-pump CABG was associated with less perioperative enzyme release from the neurological system (160), reduced embolic cerebral burden (33;35;161), and no difference (160) or less negative impact of surgery (33) on postoperative cognitive function when compared to conventional CABG. However, patient-reported outcomes were underrepresented amongst the clinical review and trial data reported (162-164), and the non-randomized studies included a potential for sampling bias due to preoperative risk assessment or the extent of multivessel disease (37;165).
Furthermore, the randomized studies did not include angiographic control for early or mid-term surgical result. There were aspects of the off-pump procedure that tempered the optimistic expectations. First, off-pump CABG appears more technically demanding of the surgeon. Secondly, although direct aortic cannulation would be avoided, one would still encounter emboli-associated phases of surgery such as during aortic side-clamping for suturing of vein grafts. Direct stimulation of the heart may lead to hemodynamic changes, for example when rotating the heart to access distal portions of the right coronary artery during the off-pump procedure (159;166-168). Finally, the possible cerebroprotective effect of moderate hypothermia during conventional CABG would not be present during off-pump CABG (169). If the two surgical techniques were to offer equal quality of the anastomoses and equal clinical efficacy, then clinically relevant differences in patient-reported outcomes might lead to a preference of one surgical technique over the other.

**Symptom relief and improvement of health status**

**Angina**

Angina pectoris is the cardinal symptom of ischemic heart disease. Angina is significant for patients in the way this symptom penetrates the experience of daily life (2;6;7). Emotional responses and adaptations to experiences of angina differ: some patients may plan to avoid angina and assume a more sedentary lifestyle, while others may adopt activities that confront the threshold for angina and pursue a more active lifestyle (7;170;171). Correlations between angina class and health status have repeatedly been demonstrated (2;172-174). Accordingly, change in angina status would be expected to translate into change in self-reported health status (133;175), although the contributions along a physical (176) and/or psychological pathway (170) are not well mapped.

While surgical revascularization usually relieves angina, CABG is a palliative and secondary preventive therapy, and the return of angina is not uncommon. After CABG, symptom relief appears to sustain through the first two years and into the long-term (177) independent of preoperative ejection fraction (175;178). With an early phase of return of angina that peaks at three months after surgery, a slower and more stable phase is probably reflective of disease and symptom progression. Studies of the prevalence of angina in a post-CABG population differ in methodology and results. In a North American multicenter study, 61-63% were free from angina at five years after surgery (18). A Swedish paper
reported one half of the patients with preoperative chest pain as being free of chest pain at 2 years after CABG; patient-reported chest pain correlating with chest pain during standardized exercise stress testing (179). While 44% of patients in the CASS study went from angina to symptom free status at 1 year after CABG (39), a more recent European study reported 95%, 82% and 61% of patients at 1, 5 and 10 years after CABG (in order) to be free from the combination of angina and positive findings on exercise stress test or radionucleotide scanning or coronary angiogram (180). Earlier observational studies cite 80% freedom from angina at five years after CABG (181).

Health status; functional status and general health perceptions

At the group level, health status has been shown to improve after surgery and convalescence (24;25;123;139), although both improvement and decline in physical, social and emotional health was represented within the group average (27;142;182). Previous descriptive research has mapped associations between patient characteristics (age, gender, education, angina class, left ventricular ejection fraction, co-morbidity, mood, sense of coherence) assessed before surgery, and short-, mid- and long term outcomes. The duration of recovery and rehabilitation, as well as postoperative health status, has been associated with age, co-morbidity, severity of disease and sociodemographic variables (125;126;133-141;183). The CABG procedure has been being offered to increasingly older patients (184-187). At the eighth or later decades, the importance of careful and individualized patient selection for surgery is highlighted by reports of a greater severity of symptoms, more comorbidity, age-related clinical (188;189) and functional outcomes variation (139;190;191).

There is some evidence that patients with worse preoperative physical as well as the mental health are more likely to improve after CABG than patients with better health status (24), although scaling/ceiling effects should be considered. Psychosocial variables have predicted psychosocial adjustment or maladjustment after surgery (183); depression before CABG has been associated with lower preoperative health status, and may predict a less favorable course of recovery after CABG (183;192). While improvement in health status has been experienced by both genders (137;193;194), preoperative gender differences in health status do not appear to diminish following CABG (195;196), and some studies have suggested female gender as a negative multivariable predictor (126;197;198). The influence of gender may include gender-specific experiences of heart disease and cardiac surgery (116;117;199-205) or gender as physiological entity favoring males after CABG (126;195;196;206).
Despite a large body of literature on health status outcomes after CABG, some areas of investigation are not well understood:

**Change in health status associated with change in observed functional performance**

In some cases, health status outcomes of CABG have been highly successful while in other cases, the attempt at palliation has not met expectations (24;27;131;140;149;182) even though the technical result of surgery may be adequate. This raises the question of how objective and subjective outcomes relate to each other, and which predictors and modifiers appear to influence these relationships. Whether or not symptom relief is achieved will be expected to influence health status (21). For instance, cross-sectional correlations of observed physical performance to physical domains of patient-reported health status are expected and have been consistently reported (207;208). However, there is little research to inform on the longitudinal association of change in exercise capacity to change in higher-level indicators of health status before and after CABG (209), and how these relationships are modified by symptom relief. Similarly, the relative significance of change in cognitive function for health status is not clear (210).

**The preoperative state of the brain as predictor of postoperative health status**

Although the heart represents the symptom-triggering organ, the presence of extra-cardiac / peripheral vascular disease has been established as a negative risk factor for the outcomes of CABG (90;211;212). There is a known association between early postoperative cognitive impairment and the number of embolic signals from the cerebral arteries during cardiopulmonary bypass (33;213). However, attempts to correlate measured cognitive performance to the patient’s intermediate or long term self report of cognitive function have not revealed a consistent pattern of covariance (214-216), leaving the hypothesis open that direct evidence of cerebral ischemic lesions might be a common denominator of cognitive performance on one hand, and perceived health on the other. Therefore, it is possible that cerebral evidence of ischemic disease (217;218) or perioperative injury (219) modifies patient-reported outcomes at the level where physical and psychosocial domains are integrated into health status perceptions.

**Overall quality of life**

There is a distance in levels of outcomes between the experience of symptoms, with a potential causal influence on functioning, health status and overall quality of life, and the
experience and appraisal of overall quality of life. Previous research addressing overall quality of life before and after CABG is of a small volume compared to studies of symptoms and health status, and the data regarding change are inconclusive. Using Cantrill’s ladder of life satisfaction, no significant change was detected at three months, 2 and 4 years postoperatively (220;221). A third study from Finland found overall single-item life satisfaction as well as happiness to decrease at 6 and 12 months after CABG (222).

A high level of overall life satisfaction has been reported to predict freedom from cardiac symptoms at 6 months after CABG (223). Revisiting the issue of the determinants of quality of life versus the experience of having a good life (61), it is not clear how and when overall quality of life assumes predictive or reactive properties in relation to CABG surgery. Life satisfaction scales do appear sensitive to major changes in life and are moderately correlated to general health perceptions, while incidental life events appear to have little impact on life satisfaction (224). If one chooses to conceptualize overall quality of life as a stable construct, then the theoretical and analytical challenge is to determine whether or not this is an individual characteristic that predicts or mediates the experience of CABG. If one, on the other hand, views overall quality of life as a perception that is causally influenced by health status and, in turn, by CABG surgery, then outcomes assessment will be incomplete without a measure of overall quality of life. A third option is to propose bidirectional relationships, where overall quality of life takes on the role of outcome as well as covariate. The clinical implication bears on advancing the precision of outcomes estimation.

**Aims of the study**

The main aim of this study was to document and interpret patient-reported outcomes, ranging from symptoms to overall quality of life, after convalescence and through the first year following on- and off-pump coronary artery bypass grafting.

Three perspectives were used to clarify the relationships between clinical predictors and patient-reported outcomes, and within patient-reported outcomes;

**A correlational and predictive perspective on the interrelations between observed and patient-reported outcomes**

The research questions were:

What is the relative importance of change in objectively measured cardiac and cognitive function together with symptom status, for self-reported health status at one year after
coronary artery bypass surgery? (Paper I)

What is the predictive ability of pre- and postoperative cerebral MRI findings on patient-reported physical and mental health at three months after coronary artery bypass surgery? (Paper II)

A comparative perspective of two distinct surgical techniques

The research question was:

Is there a clinically significant difference in patient-reported outcomes with regard to angina, health status, and overall quality of life at 3, 6 and 12 months following coronary artery bypass surgery with or without intraoperative cardiopulmonary bypass? (Paper III)

A methodological perspective on the fit of the data set to assumptions derived from a theoretical model of quality of life

The research question was:

Is the theory of a reciprocal relationship between patients’ assessment of quality of life and their appraisal of health, consistent with patient-reported data collected before and 3, 6 and 12 months following coronary artery bypass surgery? (Paper IV)

Methods

Design

This thesis represents one experimental study and a cluster of three descriptive and correlational studies. The experimental study was a single-center randomized clinical trial with longitudinal follow-up comprising four time-points. The descriptive studies followed a cohort of CABG patients over one year with self reported as well as observed data. The parent study was the experimental study; the descriptive studies analyzed patients from the same data set.

Adaptation of the theoretical framework

The complexity of the Wilson and Cleary causal pathway model (Figure 1, p.6) model includes concepts at an early stage of development, and a large number of parameters. If the 13 directional arrows were to be included for main effects, opposite effects, and
bidirectional effects, a total of $13^{13x3}$ combinations would be possible – even before considering alternative paths between constructs or the degrees of freedom to allow for each construct. Clearly, it is not feasible to test the whole model empirically. We specifically used the model as a guide, in contrast to applying the total model to the present study in a one-to-one relationship between the model constructs and available instruments. The transition from model to data collection was therefore a ‘best fit’ approach, similar to the solution used by Baker and co-workers (225). This was achieved by drawing on the main propositions put forth by Wilson and Cleary, and thereafter adapting the constructs to available health status instruments for patients’ self-report. As a consequence, the concepts general health perceptions and functional status were considered as one unit in papers I-III. In paper IV, we restricted the focus to the two concepts general health perceptions and overall quality of life.

**Study population & patient sample**

The patient population of interest was patients with ischemic heart disease, stable angina pectoris and moderate to good left ventricular function undergoing first-time coronary artery bypass surgery at the Department of Thoracic and Cardiovascular Surgery, Oslo University Hospital, Rikshospitalet. The sample of patients for this study came from South-East Norway. During the recruitment period from March 1999 to March 2002, one hundred and twenty patients between 40 and 80 years old were included and randomized to either on-pump or off-pump coronary artery bypass surgery. First patient contact and recruitment took place during preoperative work-up at the Department of Cardiology. Based on pre-study feasibility analysis, a gender proportion of 22% females was expected. Exclusion criteria were ejection fraction < 30 % and/or serum creatinine >200mmol/l, or a lack of ability to read, write or communicate verbally in Norwegian. Flow of patients through the study by intention-to-treat is illustrated in Figure 2. In addition to patients deceased or withdrawn, assessments missing in total were encountered at six and 12 months after surgery. The end points of the study were completion of the follow-up period (one year) or mortality. There was no cross-over between methods before surgery. However, seven patients randomized to off-pump surgery were converted to conventional CABG for various reasons. At one year after surgery, the overall mortality was 2 patients (1.7%), both occurring within 30 days of surgery.
Figure 2 Patient flow by surgical technique and intention to treat

Procedure

The preoperative phase was standardized for all patients recruited. Data were collected by self-administered questionnaires. A researcher conducted briefing and debriefing of data collection at hospital admission one to five days prior to surgery, and again at admission to
outpatient follow-up per study protocol at three and twelve months after surgery. Standardization of in-patient data collection included scheduling before diagnostic testing or consultation with a cardiac surgeon. A postal survey took place at six months after surgery. Timing of data collection was based on expected intervals to maximum benefit from surgery and the researcher group consensus on timing of hospital visits for follow-up and testing. The final outcomes assessment at one year after surgery was appropriate for a mixed-comorbidity group (137).

All procedures took place in an operation suite located at the Interventional Centre where intra-operative coronary angiography was possible (226). The same surgical team, involving four surgeons and four anesthesiologists, performed the surgery in both groups. On-table graft angiography was followed by graft revision if questionable quality of the anastomosis or the graft was revealed. The diagnostic and surgical procedures have been described in detail elsewhere (227) and summarized in Paper III.

**Randomization.**

In the experimental study, randomization took place after induction of anesthesia, into six equally sized blocks of 20 patients. Opaque envelopes to indicate the treatment arm were prepared by other researchers than those included in the operating teams. No changes were made regarding operating team upon randomization, and as a consequence of the timing of randomization, no patient withdrawals or inadvertent preoperative disclosures of treatment arm were encountered during this phase of the study. The study was blinded to the patients, in that disclosure of the surgical method was delayed until the time of 12 months’ follow-up. Blinding to the participant clinicians was not feasible, as the documentation of surgery and anesthesia contained information vital to the management of patients as well as chart information and text disclosing the surgical method.

**Instruments**

**Bio-physiological parameters**

Standard clinical data were retrieved from the common project database which is part of the hospital clinical information system. Clinical data accuracy in the parent study was ascertained by two physician researchers.
**Cardiac function: observed exercise capacity**

A standardized physical exercise test measured maximum physical exercise work capacity in Watt seconds, before and 12 months after surgery. This allowed for comparison of pre- and postoperative exercise capacity. On an ergometer bicycle, entry level resistance of 50 Watt was followed by an incremental increase of 50 Watt for every six minutes of exercise completed (228;229). Testing was limited by exhaustion, angina, or persistent ST-segment changes of $\geq 1$ mm below baseline recording. Cumulative work correlates well with maximum oxygen uptake (229;230), reflecting the adequacy of coronary blood flow or degree of ischemic heart disease. This protocol has earlier demonstrated good test-retest reliability (228) and moderate to strong associations with the SF-36 physical functioning subscale in patients with ischemic heart disease (231).

**Cognitive function (neuropsychological test function)**

Cognitive function represents reception of stimuli, storage and retrieval of information (memory and learning), organization and reorganization of information (thinking), and the process of communicating or acting upon information (expressive function) (232). In this study, a neuropsychological assessment presented different cognitive tests for the patients before and after CABG. Norm-based scoring of each test in the test battery adjusted for age and educational level.

The following six neuropsychological components and 10 tests were evaluated: motor co-ordination (Grooved Pegboard Test, dominant and non-dominant hand), psychomotor speed (Digit Symbol Substitution Test from the WAIS-R, Trail Making Test part A and B), attention (Digit Span Forward and Backward from the WAIS-R, Stroop Color-Word Interference Test), verbal learning and delayed recall (Rey Auditory Verbal Learning Test (RAVLT)), verbal abstraction and fluency (Similarities and Vocabulary from the WAIS-R, Controlled Oral Word Association Test (COWAT)), visuoconstructive abilities (Picture Completion and Block Design from the WAIS-R).

Preoperative scores for each test were standardized to yield z-scores (sum score minus the group mean score, divided by the standard deviation) and combined to a single sum score for each individual. At 12 months’ follow-up, the individual test scores were z-transformed relative to the preoperative mean and standard deviation. A higher score at follow-up would indicate an improvement from baseline test results, whereas a negative change would indicate a lower test score than that individual’s performance at baseline. This approach was
chosen over a dichotomous variable based on a cut-off point for cognitive decline (233), because i) a degree of arbitration beyond empirical evidence is introduced when converting a continuous variable to a binary value, ii) previous definitions of cognitive decline may yield erroneous estimates of natural variation (234), and iii) the z-score retains more information and allows for more sophisticated analysis than a binary score (235;236).

Evidence of cerebral ischemic lesions: magnetic resonance imaging (MRI)

Cerebral magnetic resonance imaging was obtained with a 1.5 Tesla scanner, using axial proton-density and T2 weighted turbospin-echo with 5-mm slice thickness and 1.5-mm slice intergap (Siemens Magnetom Vision; Siemens, Erlangen, Germany). The repetition time was 2200 ms, and the echo time was 14 ms for proton and 85 ms for T2. The images were evaluated by an experienced neuroradiologist, blinded to the patients’ clinical status and use of cardiopulmonary bypass. The presence of preoperative cerebral ischemic lesions was scored as absent, borderline (<5mm), or pathological (≥5mm) (237). New lesions present at three months’ follow-up were defined as one or more new cerebral lesions >2mm not present at the preoperative examination.

Patient-reported outcomes

Questionnaire construction

A battery approach was chosen using multiple instruments to evaluate patient-reported outcomes. Based on the study aims, a balance between detail (number of items) and respondent burden resulted in a target maximum respondent time of 45-60 minutes including pre-questionnaire briefing. As a whole, the questionnaire was inspired by a three-level approach suggested by Spilker (70) and designed to represent disease-specific outcomes at the symptoms level (angina), generic health status, and overall quality of life, consistent with our adaptation of the Wilson and Cleary model.

Symptom level: Angina

The 4-step ordinal level Canadian Cardiology Society scale was used for self-report of angina (238), with the addition of a fifth step for patients not experiencing angina. Range of the scale used was from no chest pain to chest pain with minimal exertion or at rest. Descriptors in the scale allow for recognition of a variety of angina-provoking stimuli:
physical activity, temperature changes, digesting meals, emotional distress. The CCS scale has been a reference criterion for validation studies of more recent angina questionnaires (239;240). It has been used for self-reporting in longitudinal studies (182;241-244), with a strong interrater agreement (kappa = 0.816) between patients and physicians (182). For this study, the original wording was slightly modified for self-report, and translated (forwards – backwards to Norwegian by the investigators (LM, MA)), compared to a Swedish version (242), and pilot tested for patient acceptability.

Functional status and general health perceptions

SF-36 (Medical Outcomes Study, Short Form 36 Norwegian version 1.2). Use of a generic health status questionnaire satisfied the principle that (at least) three core domains be evaluated in order to satisfy construct validity of health status: physical, psychological, and social (245). This questionnaire includes 36 items to score eight dimensions of health experienced during the past four weeks: physical functioning, physical limitations of role functioning, bodily pain, general health, vitality, social functioning, role functioning / emotional limitations of role functioning, and mental health (72). The SF-36 is comprehensive enough to have content validity with commonly accepted definitions of health (72), and has demonstrated sensitivity and responsiveness to coronary artery disease and the outcomes of CABG surgery (25), both to improvement (137) and decline (152). Scores are transformed into 0–100 scales for each dimension, where higher scores indicate better health. Construct validity and integrity of the translation process has been supported (72;246). Internal consistency (Cronbach’s alpha) for the eight subscales has been reported from 0.80 (role limitations, emotional) to 0.93 (bodily pain) in a randomly drawn Norwegian population (246), whereas in this study, internal consistency fell at baseline within 0.73 (general health) and 0.87 (physical function), and at 12 months follow-up between 0.77 (vitality) and 0.91 (physical function). Reliability has previously been reported at between 0.68-0.93 for a CABG population (247).

Two summary scores, a physical (PCS) and a mental (MCS) component summary, are derived by factorial weighting per manual of 8 subscale scores (248). In this study, a national reference population was matched for age and gender to the patient sample (246). The physical and mental component scores compare to the reference population with a mean of 50 and a standard deviation of 10 along a 0-100 scale.
Overall quality of life

As there is an ongoing debate over single- versus multi-item instruments to indicate the overall quality of life construct, two different scales were included in the questionnaire (38)p.35-37). We used one multidimensional scale as the primary indicator at this conceptual level in the experimental study, with specific items for constituents of overall quality of life. An additional single-item scale was included as a secondary indicator in the randomized trial, and also used as an alternative indicator of overall quality of life in the methodological perspective of our aims.

QOLS-N (Quality of Life Survey – Norwegian).

The QOLS-N is a 16 - item instrument measuring overall quality of life, yielding a single summation score ranging from 16-112 for all items (249). This instrument origins from a US query of healthy people concerning their quality of life (250). Across health versus chronic disease as well as across nations, factor analysis demonstrates the instrument to cover i) relationships and material well-being, ii) health and functioning, iii) personal, social and community commitment. Following translation and validation studies, psychometric data exist for Norwegian patients (251;252). Cronbach’s alfa ranged from .82-.88 in chronically ill with rheumatoid arthritis and systemic lupus erythematosus, and .86-.89 in patients with psoriasis. Test-retest reliability-coefficient was reported at .83 -.84. In this study, analysis of internal consistency at baseline returned a satisfactory Cronbach’s alpha of 0.83, increasing after surgery to 0.90 at all assessments.

Single item overall quality of life

This is a seven-step ordinal scale of overall life satisfaction, ranging from very dissatisfied to very satisfied and phrased as in the HUNT-1/North Trondelag Survey (253). A single item scale leaves the respondent free to include/exclude and weight any and all aspects of life considered important, i.e. not limited to the influence of health issues. In a population survey, the life satisfaction item has demonstrated responsiveness to the presence of major disease (diabetes) with a strong relationship to concurrent cardiac disease, as well as the adjusted response to new onset of disease (254;255). Stability over time, regardless of interim events, has in a US sample been reported at r=0.43 (256), with expectations of a higher coefficient where no major change has occurred (224). We observed intercorrelations between time-points ranging from r=0.29 to r=0.62 with the strongest associations noted at the more stable phase of health transition between 6 and 12 months after CABG.
Completion rate was excellent for this item with a single missing response amongst all questionnaires returned.

**Background and control variables**
Supplemental items and instruments were added to represent background or control variables. Sociodemographic data included age, gender, marital and work status, duration of education in years, living conditions (co-habitation vs living alone) and source of income.

Table 1 Outcomes indicators and their scales of measurement

<table>
<thead>
<tr>
<th>Concept and indicators</th>
<th>Number of items, response scale and range</th>
<th>Time points of assessment (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall quality of life</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QOLS-N</td>
<td>16 items, 7-point Likert scale (very dissatisfied / very satisfied)</td>
<td>x x x x</td>
</tr>
<tr>
<td>Single item scale</td>
<td>1 item, 7-point Likert scale (very dissatisfied / very satisfied)</td>
<td>x x x x</td>
</tr>
<tr>
<td><strong>General health perceptions and Functional status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SF-36</td>
<td>36 items, the response scale varies from dichotomous to Likert-type for each of 8 domains. Raw scores are transformed to 0-100 scores.</td>
<td>x x x x</td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angina - Canadian Cardiology Society Scale</td>
<td>1 item, five-point scale (no chest pain – pain at rest or with minimal activity)</td>
<td>x x x x</td>
</tr>
<tr>
<td><strong>Bio-physiological variables</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exercise stress testing</td>
<td>Continuous, unit = Watt seconds</td>
<td>x x</td>
</tr>
<tr>
<td>Cognitive function</td>
<td>Continuous, unit = z-score relative to baseline mean and standard deviation</td>
<td>x x x</td>
</tr>
<tr>
<td>Ischemic lesions, cerebral MRI</td>
<td>Binary: normal vs borderline or pathological ischemic lesions</td>
<td>x x x</td>
</tr>
</tbody>
</table>

Background variables included binary items for chronic diseases associated with ischemic heart disease, anxiety and depression measured with the Hospital Anxiety and Depression Scale (257), perceived amount of social support (258) and quality of contact. The
occurrence of significant life events during the study period was measured with eight binary indicators, to be used as a control variable in the randomized study (253).

**Statistical analysis**

**Overall considerations**
Data management, subscale calculation, and analysis were handled with the SPSS version 11.0 through 15.0 (SPSS Inc., Chicago IL). To avoid researcher bias during data collection, no interim analyses of patient-reported outcomes were planned before the completion of data collection. Transformation of SF-36 data to norm-based scoring used age-and gender-matched population norms from the 2002 Norwegian health survey, coinciding with the follow-up period of the present study (259).

Sample size was estimated according to the statistical power requirements of the experimental study. A two-sided alpha of 0.05 and 80% power was used for tests of difference between groups. The SF-36 manual recommendations for sample size were adopted: Assuming a drop-out of 10%, the minimum sample size to detect a difference of 10 points - corresponding to a 0.6 effect expectancy - was determined at 50 patients in each group (260). As documented in longitudinal studies of changes in SF-36 physical and mental component scales of health, the clinical interpretation of a 0.6 effect size corresponds to an interval between “somewhat more limited” and “a lot more limited” (248).

The analytical strategy addressed three general issues when analyzing patient-reported outcomes data: handling of i) missing data, ii) multiple and correlated outcomes, and iii) making a choice of analysis for longitudinal data (38;50). Specific solutions are described in papers I-IV.

**Missing data.** Regarding the SF-36 and QOLS-N, missing data were handled according to manual (248) and literature (249). For an incomplete multi-item scale, a scale score was calculated if the respondent had completed at least half of the items. Available case analysis was the initial choice for each study. This strategy is vulnerable to the influence of non-randomly missing data (50). A study-by-study decision was made as to the selection of follow-up analyses and/or imputation strategies to assess the influence of missing data.

**Multiple and correlated outcomes.** PRO research involves numerous possible outcome measures at different conceptual levels, which implies that the risk of spurious associations between variables increases for every analysis performed. Inadvertent results may be
plausible, but fail to replicate in other studies or with other data sets. The use of theory-guided analysis was a general strategy to reduce chance comparisons and clinically irrelevant but statistically significant findings (42).

**Analysis of longitudinal data.** A general linear model was used for regression analyses in papers 1, 2 and 3, where we included the baseline value of the dependent variable as a linear covariate to reduce the potential impact of “regression to the mean”; a statistical phenomenon describing the tendency for more extreme values to be followed by less extreme values at subsequent analyses (261). The baseline covariate would also take into account the expectancy for strong serial correlations between patient-reported outcomes scores.

Due to the uncertain influence of gender on outcomes, and the potential for a lack of gender balance during inclusion, gender was included as a control variable in papers I-III. Other covariates and factors were added based on clinical judgment, theory and the research literature, as deemed appropriate with regard to the rationale for the study.

**Variable description and analytical strategy by research perspectives**

**A correlational and predictive perspective on the interrelations between observed and patient-reported outcomes**

**Paper I**

In a multivariate hierarchical regression analysis, we determined the association of three predictor variables: change in cognitive function, observed exercise capacity, and improvement of angina, to the SF-36 physical and mental health summaries, entering the predictors in a sequence determined by the causal pathway model. Two-way interactions were tested for angina status, change in observed exercise capacity, and gender. A sensitivity analysis was performed to evaluate the influence of missing data.

**Paper II**

Analysis of covariance determined the association of pre- and/or new postoperative cerebral ischemic lesions to change in the SF-36 physical and mental health summaries, adjusting for preoperative health status, use of cardiopulmonary bypass, gender and improvement of angina. Two-way interaction effects were tested for preoperative cerebral MRI status and surgical method.
A comparative perspective of two distinct surgical techniques

Paper III
The experimental variable in this randomized study was surgical method: on-pump or off-pump CABG. The dependent variables were three separate constructs: symptom/angina, health status, and overall quality of life. All comparative analyses were by the intention to treat principle. On the condition that the two groups did not differ significantly in outcomes as determined by angina classification, analysis of covariance models were estimated using surgical group and gender as independent variables, and the baseline value of each dependent variable as a covariate. Interaction terms for gender and surgical method were tested. Supplemental and planned outcomes, sleep and sexual difficulties, were included in separate analyses to secure sensitivity to areas of health status where the SF-36 does not include explicit items. The initial available case analysis was repeated with a data set where we applied imputation strategies for cross-sectional and longitudinal data (262;263).

A methodological perspective on the fit of the data set to assumptions derived from a theoretical model of quality of life

Paper IV
To evaluate bidirectional causal effects, conventional multiple regression is not appropriate and therefore, longitudinal path analysis was applied with structural equation modeling of single indicators (264). The Wilson and Cleary causal pathway model was used to specify relationships (21) between general health perception and overall quality of life - as illustrated in paper IV - with separate analyses for each of the two overall quality of life instruments in this study. Complete sets of data were required for this analysis over four time-points.

Ethical considerations
The study was conducted in accordance with the principles of the Helsinki declaration. All patients provided voluntary, written and informed consent. The Regional Committee for Medical Research approved the project on 05-23-1998. For patient safety, qualified follow-up from the Department of Psychosomatic medicine was available, should unexpected psychosocial distress appear as a result of the study. Our expectations were in the opposite
direction, as data collection may represent an additional therapeutic benefit (265) by allowing the patient to express his/her concerns systematically and without provider bias. When scheduling research data collection before a clinician interview, there may be a concern of loss of clinically relevant information if a patient feels that issues already have been discussed, and that no further mentioning is needed. Patients were encouraged to approach their surgeon or nurse with any concerns expressed, and the role of the researcher was clarified when patients provided oral or written information that was recognized as a clinically relevant issue.

The patients were in a dependent situation meaning that the motivation for surgical therapy could threaten the integrity of a voluntary consent to an extensive set of tests and interviews in addition to standard surgical procedure. The research team and patient coordinators planned for additional preoperative hospitalization and duration of follow-up visits to reduce the intensity of patients’ schedules. Questionnaire length and content was pilot tested for patient acceptance in order to minimize patient burden and enhance adherence to the study. The loss of data experienced suggested that patients did feel empowered to exercise their rights to withdraw from the study or decline participation in individual diagnostic tests, if the burden exceeded their level of acceptance.

Results, summary of main findings

At the group level, surgery was followed by improvement in angina and health status. At one year after surgery, eighty-one percent of responding patients reported their health as ‘somewhat better’ or ‘much better’ than a year ago. Compared to national population norms matched for age and gender to the patient sample (259), preoperative health status was significantly lower while the scores at one year after surgery fell within half a standard deviation of the population mean. Overall quality of life, measured with the QOLS-N, was above unadjusted national reference data (252) before surgery as well as at one year after CABG, and the change after surgery was not statistically significant\(^1\).

\(^1\) Paired t-test, \(p=0.071\), \(n=113\)
The correlational and predictive perspective

In the first study, we characterized the impact of CABG on self-reported physical and mental health, with adjustment for change in cardiac function, change in cognitive function, and symptom relief. As expected, physical and mental health had improved significantly after surgery, and the multivariate regression models explained 33% of the total variance in physical health (adjusted $R^2$), and 27% of the total variance in mental health. Improvement of angina, reported by 75.6%, was associated with improvement in physical health in the range of half a standard deviation ($\beta 0.23, p=0.012$). Change in observed exercise capacity independently accounted for 9% of the variance in physical health ($\beta 0.42, p=0.001$). Change in cognitive function was significant for mental health ($\beta 0.52, p=0.007$), but not physical health. Graft occlusion, present in 22 of 82 patients, was not significant for health status.

The second study found that preoperative MRI evidence of cerebral ischemic injury, combined with the use of cardiopulmonary bypass, was predictive of postoperative physical health status at three months after surgery. The analysis, adjusting for preoperative physical health, demonstrated a significant interaction effect of preoperative cerebral ischemic injury and use of cardiopulmonary bypass ($F = 9.07, p = 0.003$), which was independent of age or gender. The estimated mean difference between on-pump groups defined by MRI status was 8.2 points on a 0-100 scale, implying a clinically significant difference. No significant independent effects on health status were found of baseline MRI or new cerebral lesions at three months. In terms of risk factor importance, cerebral MRI was a more specific predictor than age for physical health after on-pump coronary artery bypass surgery.

The comparative perspective

In the third study, there were no significant differences between surgical groups in health status or overall quality of life explained by surgical procedure, neither cross-sectionally nor longitudinally. The randomization was successful regarding age, symptoms, co-morbidity, and surgical characteristics, while a difference in gender distribution was present. Both groups experienced a median of 2 CCS-classes relief of angina at 3 months, maintained throughout follow-up. Paired t-tests revealed significant improvement on all SF-36 subscales at three months after surgery, with the exception of physical role functioning in the on-pump group. Overall quality of life scores were stable in both groups. We did not identify an interaction effect of gender and procedure. The longitudinal influence of gender
was significant in four Short Form 36 subscales: physical functioning, bodily pain, and role limitation due to physical or emotional problems. Follow-up analysis revealed that the composite SF-36 mental and physical summary scales, used as references for sample size calculations, confirmed a finding of insignificant group mean differences at 3 months after surgery\(^2\). We concluded that on- or off-pump coronary artery bypass surgery led to comparable patient-reported outcomes.

**The methodological perspective**

The fourth study tested for fit of the data to the Wilson and Cleary causal pathway model suggesting reciprocal (bidirectional) causal paths between general health perceptions and overall quality of life. General health perceptions were measured with the General Health subscale of the SF-36. Overall quality of life was measured with i) a single question regarding life satisfaction and ii) the multi-item Quality of Life Survey – Norwegian version. We used longitudinal data to model time-delayed (lagged, cross-lagged) and concurrent causal paths over four time-points of assessment from before surgery to one year afterwards. Acceptable model fit of the data was obtained for bidirectional causation between general health perceptions and overall quality of life. Regression coefficients changed over different phases of health transition after surgery. Serial correlation accounted for much of the variance within variables over time. Based on the results of structural equation modeling, we concluded that overall quality of life could both influence and be an outcome of general health perceptions after CABG surgery.

**Discussion**

Overall, the present investigation confirmed the expectations of CABG surgery regarding the ability to improve, at the group level, symptoms and health status, with the majority of health status changes occurring through the first six months after surgery, and a more stable period towards 12 months after CABG (154;266). A positive health transition was reported by 81% at one year after CABG, which is somewhat less than 92% reported in an Australian

\(^2\) At 3 months after surgery: ANCOVA, df\(_{4,109}\); PCS 1.83 points in favour of off-pump (\(p=.349\)), MCS 1.87 points in favour of on-pump (\(p=.356\)). Longitudinally over 12 months after surgery: ANCOVA, df\(_{4,102}\); PCS 1.67 points in favour of off-pump (\(p=.271\)), MCS 1.31 points in favour of on-pump (\(p=.402\)).
study of 123 patients with comparable age and gender mix (267). This discussion and interpretation of findings will follow the same sequence as the perspectives of our research questions.

The correlational and predictive perspective

In two descriptive studies, the common theme was a search for theoretically founded, statistically significant, and clinically interpretable links between observed predictors and patient-reported outcomes. The variance in individual outcomes after CABG was greater than what age, gender, and preoperative health status could explain. Two main findings from our studies may have clinical and scientific value: First, our results provide empirical evidence to differentiate the paths of influence from objectively measured surgical outcomes towards symptoms and physical capacity. Secondly, the data suggest that a theory of preoperative cerebral vulnerability (268-270) may be extended to be predictive of patient-reported outcomes.

A concept of successful surgery may cover multiple related elements such as completeness of revascularization, relief of angina, and objectively measured functional improvement without persisting adverse neurological outcomes, all of which are expected to result in improved health status as experienced by the patient. In multivariable analysis and at one year after surgery, change in cardiac function and symptom relief each explained significant and unique variance in the change in physical health following CABG. Representing a functional benefit of CABG surgery, the group mean improvement in exercise stress test capacity corresponded to a moderate effect size of 0.4 - 0.5 (271). Previous research has identified small to moderate, but statistically significant, associations between observed exercise capacity and health status; observed exercise capacity is most strongly associated with mobility, physical limitations and pain (208;231;272;273). Variations in study methodology include different testing protocols, timing of assessments in the longitudinal studies, and different patient questionnaires. Our analysis extends previous studies by documenting a limited overlap between change in exercise capacity and symptom relief in their association to change in physical health. As the benefits of CABG on symptoms and coronary reserve flow do not run parallel, angina classification alone does not explain changes in physical health status. Moreover, there appears to be only a modest association of graft patency per se to health status. Many surgical factors influence the degree of revascularization and the number of grafts. The final decision on target vessels is a balance
between technical possibilities and limitations influenced by interpretation of the
preoperative angiogram, direct visual inspection of the coronary anatomy during surgery,
and the graft material available. A proactive strategy may lead to a larger number of grafts,
targeted at vessels including those where a marginal benefit in flow may be expected. A
conservative strategy with fewer distal anastomoses may seek to limit the surgical trauma by
a shorter duration of surgery and cardiopulmonary bypass.

As angina and physical exercise capacity each appear to contribute significant and unique
variance to physical health, it is suggested to include both symptom status and an objective
or subjective indicator of physical capacity in pre- and postoperative outcomes evaluation.
A standardized physical functioning questionnaire may be a low-cost / high validity
instrument to elicit clinically sensitive, actionable and everyday relevant data to promote
patient participation in preoperative decision-making and postoperative evaluation. Reports
are few and mixed as to whether health status assessments lead to improved patient
satisfaction and outcomes (274-276). However, there is evidence from the oncology
(277;278) and general practice context (279) that the use of standardized patient-reported
health status assessments facilitates the discussion of health status issues and can heighten
clinicians’ awareness of their patients' situation.

The experience of angina relief after CABG differs between patients. One fourth of the
patients reported anginal pain at 12 months after CABG, and had significantly lower
physical and mental health scores than patients not reporting angina. While our results are
aligned with the existing literature in support of an expectation for symptom relief following
CABG (180), it seems appropriate to educate patients on the difference between a ‘cure’ for
angina and the palliation offered by CABG surgery (115). Furthermore, some patients will
experience incomplete symptom relief or a return of symptoms (39;179). There are
mediating and confounding issues regarding self-reported angina that may be clinically and
scientifically important. The proportions of pre- and postoperative angina vary widely
between studies, even though grading usually follows the Canadian Cardiovascular Society
scale (238). Beyond different inclusion criteria, methodological differences between studies
include the selection of rater (patient or physician), the time frame of assessment (worst
level, average over time, or today), and the process of appraisal (before clinical evaluation
or a result of evaluation). A relevant distinction may be made between self-reported angina
(172) - the subjective appraisal of angina as perceived by the patient - and the physician’s
labeling and classification of chest pain as angina following the patient’s narration of pain
symptoms (180). This distinction is not always evident in the literature and may contribute to explain part of the variation between studies; differences may be in the direction of a higher as well as a lower prevalence of chest pain compared to objective indicators of cardiac ischemia.

At the individual level, pain that is interpreted as angina represents both a sensory and an emotional experience (280). Different mechanisms and interpretations of chest pain may be present. Chest pain that is perceived as angina, takes on the meaning of angina for the individual patient, until this perception is re-evaluated through experience or counseling (170;281). Also, the emotional response to chest pain/angina is individual, can change, and may itself modify the experience and behavioral response to chest pain/angina (6;7;282;283).

It is notable that chest pain appears both as cause and consequence of CABG (284). As cause, anginal pain remains a hallmark of coronary artery disease. As consequence, both an initial postoperative chest pain and the possibility of long term post-CABG pain has been reported (285). At the time of study design, the prevalence and experience of chronic non-anginal chest pain (285-289) was uncertain. Post-CABG pain syndrome is gaining a research interest and may affect one third of the patients, although the reported prevalence in different studies ranges from 7.5% (289) to 56% (285). Three patterns of pain have emerged: a left-sided pain probably related to harvesting of internal mammary artery, a midline scar pain, and a more uncommon right-sided pain (285). For patients’ physical activity level as well as mood, associations to misconceived or maladaptive beliefs about angina have been demonstrated (170). Thus, not only is the evaluation of post-CABG chest pain important from a differential diagnosis perspective, but the impact on mood and functional status may be modified by appropriate patient education.

Previous research indicates a risk of adverse neurological consequences of CABG surgery in certain patient groups (14;290-292). We found that the combination of preoperative evidence of cerebral ischemic lesions and intraoperative cardiopulmonary bypass predicted less improvement in physical health status at three months after CABG. Cerebral vulnerability may be anatomical, indicated by cerebral ischemic lesions (MRI), or functional such as with limited cerebral reserve (below average cognitive function). In the first case, we found that the predictive value was related to physical health at three months after surgery and was dependent on whether intraoperative cardiopulmonary bypass was used. Age was not significant in this context. It should be kept in mind that no direct association
can be assumed between the degree of coronary and cerebral arteriosclerosis; it has been demonstrated that coronary artery disease correlates with external carotid stenosis, but not stenosis of the internal carotids (293). There is indirect evidence for the use of cardiopulmonary bypass and manipulation of the ascending aorta as specific risk factors for new postoperative cerebral MRI-lesions suggesting ischemic changes after CABG (294). The degree of aortic manipulation during surgery appears to influence the extent of embolization and postoperative stroke (295). Due to the low incidence of postoperative stroke, registry data will remain a central method to evaluate this outcome; preoperative neurological events appear to be predictive of postoperative events (296). Controlled clinical studies must rely on other indicators of cerebral perfusion with unknown or lesser impact on patient-reported outcomes. Although our results will need confirmation in prospective studies, it is suggested that evidence of cerebral arteriosclerotic disease may be a risk factor to consider over chronological age, if off-pump CABG is an available option for revascularization.

We found that both preoperative cognitive function scores and change at 12 months after CABG were predictive of mental health. This occurred regardless of the use of intraoperative cardiopulmonary bypass. It appears that cerebral recovery from transient effects of surgery is completed at one year or earlier, and also that the use of cognitive function scores that allow for improvement as well as decline may be important to interpret CABG outcomes. Studies using control groups suggest that the negative influence of CABG and cardiopulmonary bypass may have been overestimated (297-299). Co-researchers on the present thesis found that the raw count of Doppler-detected intraoperative embolic signals – where greater counts are demonstrated during on-pump CABG - were only predictive of postoperative cognitive function when accounting for preoperative evidence of cerebral ischemic lesions (269). Using diffusion-weighted cerebral MRI to detect acute cerebral ischemic changes after CABG, Cook and co-workers did not observe a significant association to a decline in cognitive function, leading to the conclusion that underlying patient factors rather than new ischemic changes were of importance for cognitive function (300). Of note, the impact of change in cognitive function for self-reported health is not well understood. Although a significant cross-sectional association was reported between cognitive function and quality of life at five years after cardiac surgery – receiving much attention (102), this study could not address whether a change in cognitive function was associated with a corresponding change in quality of life. Longitudinal studies to combine
measured cognitive function and patient-reported health status/quality of life indicators are scarce, and the diversity of findings in two existing studies (reference (210) and paper I of this thesis) suggest a need for more research in this area. It remains a challenge for the comparison of studies that the degree of standardization of patient-reported outcomes before and after CABG is low, regarding the constructs to be measured, the methods to use, and the timing of assessments (8).

We included gender as a control variable in all studies as an individual characteristic, with no specific hypotheses indicating a predictive, effect-modifying, or confounding influence. The influence of gender was found to be sensitive to the selection of analysis. Univariate and cross-sectional associations of gender to health status after CABG changed strength and direction when adjustment for baseline health status was introduced. Furthermore, the role of age in this sample and analysis was of negligible importance. Gender remains a controversial issue in the CABG literature. Some researchers see gender as a marker of more comorbidity, advanced disease and poorer health status before surgery (301;302), or that there are gender inequalities regarding perception of health and symptoms (201;202) or access to health care and disease management (303;304), while others maintain gender as an independent risk factor for clinical variables during the perioperative period or observe gender differences during the course of rehabilitation (126;157;204;205;305-307). The difference in social roles have been proposed as a contributing factor, where domestic responsibilities may account for a larger discrepancy between task expectations and physical capacity, while at the same time being associated with more physical tiredness and hence better quality of sleep. Several authors assert that females have less symptomatic relief and lower functional status than men, also when adjusting for baseline (126;272;308). However, Oparil (309) maintains that risk factors and lifestyle modification explain the observed differences, and that the future may correct current underdiagnosis and underutilization of therapies in females. Koch (194;310) asserts that prevalence of risk factors, and not gender per se, is predictive of short- and long-term survival after CBG. Females may be at a disadvantage with some exceptions; the relative hormonal protection regarding arteriosclerosis before menopause and a lower rate of arteriosclerosis progression in vein grafts after CABG (311). Gender-specific guidelines for perioperative management have been suggested (312). Thus, the absence of a significant impact of gender as a control variable in our analyses should not be interpreted as evidence of the lack of importance of gender. There is a need for research designs that recruit and stratify both genders in
sufficient sample sizes to evaluate patient-reported outcomes related to post-menopausal female health, gendered cardiac symptomatology, and possible inequalities regarding access to health care services.

The experimental perspective

The key finding of our comparison of surgical methods was that there was no clinically significant differences in patient-reported outcomes with regard to angina, health status, and overall quality of life 3, 6 and 12 months following coronary artery bypass surgery with or without intraoperative cardiopulmonary bypass. This experimental study included radiological evaluation of the technical result of surgery, intraoperatively as well as at follow-up. Clinical and radiological outcomes were comparable, similar to the findings of other studies of patient-reported outcomes that included angiographic evaluation (313-315).

As of June 2009, there are eight randomized studies of patient-reported outcomes before and after on- or off-pump CABG; two single-surgeon trials (313;315), one multi-center trial represented with three papers (150;266;316), and three single-center studies (317-319). Our study is one of two to include self-reported angina scores, finding comparable results between surgical groups (320). Regarding health status outcomes, seven of eight studies shared the use of the SF-36 questionnaire. Statistically relevant (p<0.05) differences between surgical groups were reported in 4 instances which involved the social functioning subscale (313;318) or role limitations due to emotional (317) or physical problems (150). These exceptions did not indicate a consistent and convincing association to surgical method. Across all eight studies, less than 5% of 104 health status comparisons at different time points suggested a difference by surgical group, which may be explained by chance alone.

Two of the randomized studies report on overall quality of life as conceptualized in the Wilson and Cleary model, finding no significant differences between surgical groups (315;318). We observed a longitudinal stability of this construct despite statistically and clinically significant improvements in health status. In the remaining studies, the operational definition of quality of life appeared restricted to health status or health-related quality of life; The EuroQoL questionnaire includes an overall single-item scale that specifies ‘health today’ as the stimulus (150;313;321;322); the Seattle Angina Questionnaire contains a quality of life subscale to indicate “the burden of coronary artery disease on patients’ quality of life” (239;320).
In addition to the randomized trials with a preoperative assessment of patient-reported outcomes, three randomized trials compared postoperative assessments only of health status (317;320;323), the latter study recently reporting long-term follow-up (324), and all papers concluding with similar health status outcomes between surgical groups. Comparing randomized studies of patient-reported outcomes to reports of clinical and objective functional outcome measures, the body of literature appears aligned in the overall lack of differences between surgical methods. Cognitive function does not appear different by surgical method, although concerns of statistical power have been raised (150;266;325;326). Increasing the possible effect size by including a more high-risk sample than in our study, no difference in cognitive function was found at 3 months (327). In the absence of differences in cognitive outcomes, an expected benefit of off-pump CABG for patient-reported outcomes is less probable. However, the on-/off-pump question is still open to debate, and there may be alternative pathways that affect recovery and patient-reported outcomes. In a registry study of 49830 patients, off-pump patients had a lower incidence of stroke and respiratory complications, but also less freedom from a need for subsequent revascularization than their on-pump counterparts (328). Another registry study found a lower incidence of stroke and operative mortality amongst 12812 patients, but comparable survival in a 10-year follow-up (329). Randomized trials suggest that the systemic inflammatory response – clinically relevant for the association to short-term complications and length of hospital stay - is less intense with off-pump surgery (330;331), possibly due to a difference between surgical methods in complement activation (332). A meta-analysis found a lower prevalence of postoperative atrial fibrillation and need for intensive care services in the off-pump group compared to conventional CABG (333). As patients can achieve an excellent outcome with either procedure, the outcome for individuals may quite possibly depend more on factors other than surgical method (334).

In conclusion, current evidence from available randomized controlled trials indicates that CABG performed either on-pump or off-pump improves patients’ symptoms and health status in the short- and mid- to long term, and that there is no firm evidence of clinically significant differences between surgical groups regarding patient-reported outcomes. The question remains open regarding the effect of CABG on overall quality of life; the causal mechanisms are largely unexplored, the concept of overall quality of life is still ill-defined, and operational definitions demonstrate great variation ranging from angina score to subjective well-being. This will remain a challenge for meta-analyses and review studies.
The methodological perspective

The methodological challenges of patient-reported outcomes research include specification and testing of the relationships between concepts used to describe the determinants of quality of life and the domains of quality of life (23;38;38;44;50). In the fourth paper of this thesis, we empirically examined theoretical and causal links between the concepts of health and overall quality of life. Our dataset was consistent with the existence of bidirectional causal effects, meaning that overall quality of life can both be a cause and an outcome of general health perceptions after CABG. In clinical terms, these results indicate a zone where patient (state or trait) characteristics interact with the impact of surgical outcomes. Both “bottom up” and “top down” mechanisms may apply, suggesting that knowledge from the social and health sciences may augment surgical results by activating resources within or available to the patients. In patient counseling, clinicians need to consider whether the use of an abstract label such as ‘quality of life’ promotes mutual understanding or not. This challenge may come when sharing information with patients before decisions of therapy (335), or when individual patient preferences for a lesser degree of detail - due to coping style or capacity for understanding - draw discussions towards more abstract and less specific concepts such as ‘quality of life’ (336). The Food and Drug Administration has responded to claims of effects on quality of life in advertising, assessing that the term 'quality of life' appeared “unsatisfactory because it is too broad and nonspecific to describe a treatment outcome” (20). Symptoms are symptoms, side effects are side effects, and physical/mental/social health is different from overall quality of life.

We concluded that unidirectional causal models are inadequate for analysis of the effect of CABG on overall quality of life. This suggests two important consequences for the interpretation of cross-sectional and longitudinal data: First, overall quality of life perceptions should be assessed in clinical trials and longitudinal research in order to be documented and - if possible – statistically modeled. In clinical trials, researchers should assess the comparability of groups regarding overall quality of life. If not equal, then statistical adjustment may be attempted, with explicit assumptions of the role allocated to this variable. In the absence of sample size or expertise for adequate statistical models, it may be appropriate to acknowledge this as a limitation when reporting general health perceptions. Secondly, a conceptual blurring of symptoms/health status and overall quality of life should be avoided. Although health may be amongst the determinants of quality of life, health is limited as an indicator of quality of life. More stringent use of concepts is
desirable not only from a philosophical perspective, but also for construct validity in empirical research. For clinical purposes and patient counseling, the normative associations arising from use of the quality of life concept may indicate greater expectations of surgery than what is supported by empirical data (20).

Our study is an early and limited study of bidirectional relationships within the Wilson and Cleary conceptual framework, and further empirical validation is needed. However, the findings represent a step towards more restrictive use of ‘quality of life’ as a common label for patient-reported outcomes. Clinical researchers, seeking sensitive and responsive measures of interventions, tend to centre on outcomes that are causally more proximal to the direct influence of health care interventions. Thus, researchers may apply the label “quality of life” to items that in fact represent general health perceptions (the EuroQoL-5D e.g. (150) or an aggregate of disease burden and overall global evaluations of health and life satisfaction (Quality of Life Index - cardiac version, e.g. (337)) or satisfaction with care and burden of disease (Seattle Angina Questionnaire (SAQ), e.g. (320). Our findings question the conceptual validity of this tradition in reporting. The challenge of consistency in operational definitions is not a unique feature of CABG research (338). If the relationships of concepts are explicitly modeled, then critique and development of theoretical and analytical issues is possible. Without a theoretical framework, even the comparison of results using different instruments remains difficult. Greater differentiation of concepts may promote further development of key words used in publication databases, which, in turn, will facilitate the conduct of systematic reviews (339).

In the present study, indicators of overall quality of life were selected for their ability to be related to, but conceptually and empirically different from – subjective health status (21;22;70;340). We discovered during the course of this study that the correlation coefficient between the two instruments was only moderate ($r=0.44$ to $0.52$), indicating a possibility that different constructs were being measured (341). In paper IV, we pointed out the differences associated with instruments associated with a “top down” or “bottom up” approach to overall quality of life. Some further discussion may be added.

One philosopher argues that the overall notion of quality of life can be understood from three broad theories; one hedonist perspective centering on happiness or satisfaction, one perspective consisting of the satisfaction of people’s desires or preferences, and finally a perspective that values the realization of specific, explicitly normative ideals such as individual autonomy and self-determination (342). In relation to health care, it is suggested
that independent place be given to all three contributions or perspectives rather than to identify a single and unifying theory to guide an adequate and overall account of the quality of life (342). Our overall quality of life instruments may satisfy the first and last criterion: the items clearly elicit scores of satisfaction, and the instruments are constructed in a way that preserves the values of individually oriented communities. However, the two instruments differ in their approach to weighting of the importance of separate aspects or domains of quality of life. A single-item scale leaves full freedom to the respondent, but offers no insight into the process for the researcher. The QOLS-N scale weights all items equally, as opposed to allowing for respondent weighting (343). It is possible that part of the unique variance of each instrument is related to this difference in flexibility for the cognitive process of weighting.

A second explanation concerns the relationship of life satisfaction to quality of life. In the paper proposing the Wilson and Cleary model, the authors provide a unidimensional definition of overall quality of life – a stable synthesis of a wide range of experiences and feelings that people have (21) p.62, which we interpreted towards life satisfaction (60). Recently, two long-standing but separate research traditions – one investigating subjective well-being (344) and the other quality of life (345) – appear to be converging conceptually (346). In this development, cross-cultural evidence indicates that life satisfaction is a substantial component of quality of life as well as subjective well-being, although life satisfaction is insufficient to fully explain either (346). Thus, in light of the development towards a future consensus on overall quality of life/subjective well-being, one may criticize a lack of comprehensiveness in both of the overall quality of life instruments used in this thesis, related to their ability to represent the latent concept. In the absence of empirical data on commonalities and differences related to a potential third criterion, it is difficult to discuss in which areas common variance is absent. It is possible that state aspects of overall quality of life, such as mood, are significant in the context of coronary artery disease (192).

In conclusion, the support for complex and bidirectional relationships between health perceptions and overall quality of life indicate that several qualifiers need to be satisfied when considering the use of overall quality of life as an outcome: the causal relationships need specification, as do the possible modifying paths. Finally, the conditions for when the specified paths apply – or do not apply – are helpful for analysis and interpretation.
**Methodological considerations**

This section presents a critique of the scientific quality of this study. Central issues in patient-reported outcomes research are the theoretical anchoring of relationships between concepts and between concepts and indicators linking conceptual and operational definitions, the handling of missing data, and strategies to handle multiplicity of outcomes (42).

There are two aspects of the Wilson and Cleary model that are well aligned with the present study aims. First, an explicit ambition of the model is to link the natural and social sciences, from the level of bio-physiology/objective measurements to the level of subjective perception, and represent a framework from which empirical studies may refine the model. Studies of heart surgery patients have confirmed associations cross-sectionally as well as longitudinally, strongly suggesting that biopsychosocial mechanisms be parts of a single general multifaceted process influencing recovery of health (223). Second, the introduction of directional arrows in the model offers a starting point from which causal hypotheses might be assumed or tested. Explicit modeling addresses the potential problem of multiple and correlated outcomes in patient-reported outcomes research (42).

**Validity**

Validity refers to the relationship between concept and indicator, or the degree to which the indicator measures what it intends to measure (347). Validity is also an issue in the design of the study, and how well the conduct of a study matches the purpose.

**Design**

For all study aims, a longitudinal design with preoperative baseline data was appropriate, allowing for the assessment of change with statistical adjustment for differences at baseline. Several features of the study aimed to reduce variation in surgical quality. Intraoperative coronary angiography was used to ascertain technical quality of the anastomoses and prevent short-term graft failure (314). Although a single-surgeon study would add to the level of standardization, such a study may be vulnerable to bias due to referral patterns (334). The team of surgeons had varying experience with the off-pump procedure, all acquainted with this technique during the initial animal studies and patients treated in the preparatory phases prior to randomization, and all assisting each other in the inclusion period. Others have addressed the issue of learning curve by comparing operations
performed by two trainees under supervision to operations performed by an experienced consultant surgeon. Operative morbidity and mortality were found to be similar, although trainee surgeons were less likely to operate on patients with unstable angina or cardiac dysfunction (348). The single-center context provided control for differences between multi-center sites regarding protocol adherence and clinical tradition.

There was minimal drop-out from recruitment to inclusion. At the study site, patients are commonly discharged to the patients’ local hospitals on the third postoperative day, resulting in more variation of in-hospital rehabilitation just prior to discharge to the home setting. We did not standardize or control for differences in the rehabilitation period such as participation in cardiac rehabilitation efforts, or the frequency and content of follow-up by a primary care provider. This is a limitation of our design. However, two Cochrane reviews have not been able to demonstrate consistent effects of cardiac rehabilitation on cardiac mortality (349) or quality of life (350), although individual studies do support such interventions for stress management and functional status. A recent study has compared the outcomes of cardiac rehabilitation for on-pump and off-pump CABG with regard to performance measures and patient-reported outcomes, finding no significant difference between surgical groups (351).

The lack of ability to blind treatment allocation also limits our design, possibly affecting hospital personnel as well as patients. Allocation to the preferred treatment in randomized trials is associated with an augmentation of effects (352), and in hindsight, any patient preferences for on- or off-pump surgery could have been enlisted and entered into control analyses. Features of this study to reduce bias were the delayed randomization and efforts to avoid untoward disclosure of therapy arm.

Block randomization offered a degree of control for effects of a prolonged inclusion period, such as skills and technology development, and allowed for minor changes in the protocol during the study without biasing the randomization. We did not stratify by gender and relied upon the randomization process to be successful in the allocation of this variable to either surgical group. Stratification by gender would have improved on the balancing of the two surgical groups and might have increased the precision of our correlational and predictive analyses.
Timing of assessments

The first two postoperative months were not assessed in this study, which limits our ability to draw conclusions on the period of early convalescence. A data collection on the third postoperative (ambulation, nutrition, pain) day took place, but initial analysis revealed that hospital routine appeared to confound the gaps between rapid or slow patient progression. Additional follow-up was beyond the means of this study.

The time-point at three months sampled the third postoperative month, due to a four-week time frame in the questionnaire. Data collection between the time of surgery and 2-3 months afterwards might have captured more variation between groups. Van Dijk reported SF-36 results from a randomized comparison of on-pump versus off-pump CABG at 1 month after surgery, observing improvements on five of eight SF-36 subscales but no significant difference between surgical groups (316). Other researchers have demonstrated – in non-randomized designs – that high-risk high-vulnerability patient groups might benefit from off-pump CABG in terms of ease of recovery and lack of complications (353).

Power

The sample size was based on power calculations for the comparative study of on-versus off-pump CABG (354). An overall difference in impact on physical and mental health was considered, as it was not possible to determine a specific domain or subscale of the SF-36 as the most sensitive to the impact of method. The concept of a Minimally Important Difference illustrates changes that may be smaller than considered for our power calculation but still clinically meaningful; this is defined as the smallest detectable difference that is perceived by the patient, or that would lead to a change regarding management of disease (355;356). While a Minimally Important Difference may be incorporated as a feature of a randomized trial (357), the smaller the effect size, the greater the requirements of sample size or distribution characteristics.

Sample characteristics

There are differences between the 19 counties of Norway as to the number of heart surgeries per 100,000 inhabitants, which may be related to the prevalence of ischemic heart disease as well as different referral patterns. The South-East of Norway (this study) was in 2004 placed in the mid-range with 122 surgeries pr. 100,000 inhabitants (12), and the study procedures were performed at a teaching hospital with more than 1000 annual heart surgeries (12).
Compared to national data for the year 2002, the mean age in our sample (64.5 years) was comparable to the mean age for adult open heart surgery as a whole (65.7 years), while the national 30-day mortality after CABG was 1.5% compared to 2% in this study. The data suggest little selection bias within the inclusion criteria. The drop-out rate was low and cases were accounted for (figure 2). Similar to the hospital’s elective adult heart surgery population, patients included were able to read, write or communicate verbally in Norwegian.

Compared to the general Norwegian population – unadjusted for specific diseases - the preoperative disease burden of our patient sample was evident from a significantly inferior health status, also in domains of health beyond those of primarily physical content. The improvement that exceeds the population norm scores in the domain of bodily pain at 12 months was notable, and in agreement with the observations of a population from the middle part of Norway at three years after CABG (158). The SF-36 bodily pain domain score reflects to which degree pain has interfered with daily activities at home or at work, as well as the amount of pain during the last four weeks. As the general population has an over 24% prevalence of chronic pain (duration > 3 months) (358), the shift in group characteristics after CABG is a plausible explanation for the comparatively lesser pain limitations.

**Selection of instruments for the questionnaire**

Validity is strengthened when the measures used are appropriate for the patients, setting, and intervention under investigation (359;360).

The angina scale (CCS) used in this study queries the absence or presence and triggering level of angina pectoris (chest pain). An expansion of the questionnaire would be necessary to document and control for pain experiences perceived as angina but bearing the characteristics of non-anginal chest pain. For the randomized study, this limitation was of lesser importance as long as the randomization appeared successful. Interpretation of the descriptive studies should bear in mind that only the cardinal symptom of ischemic heart disease – angina pectoris – was queried directly. Moreover, we did not collect data on the frequency of angina, which may be relevant for health status scores (239).

It may be asked whether a disease-specific questionnaire would have been more appropriate for outcomes at the level of symptoms and functional status (245). During the planning phase of this study, no treatment-specific questionnaires were available (361). We
considered three disease-specific – but not treatment-specific - questionnaires for the instrument battery (239;242;362). Respondent burden, conceptual inconsistencies, and the desire to reduce interaction effects between multiple instruments suggested against inclusion of more than one health status questionnaire. We noted an overlap of domains between the disease-specific instruments and the SF-36 on all concepts and dimensions to be reported, and considered the conceptual development of the SF-36 as more solid along with the fact that normative data for the Norwegian population were available as a benchmark for the efficacy of CABG (363). Moreover, the SF-36 includes positive expressions as well as limitations of health, and features well-documented evaluation of the clinical relevance of point changes in scoring. It has been suggested that the SF-36 has a lesser discriminative ability between different angina classes (240). Liang distinguishes the terms “sensitivity to change” (the ability of an instrument to measure change in a state irrespective of whether it is relevant and/or meaningful) and “responsiveness” (the ability of an instrument to measure a meaningful or important change in a clinical state) (364). The overall change in health on all subscales as compared to the population norms suggests that adequate instrument responsiveness was present in this thesis.

In Paper I and II, we used the SF-36 physical and mental health summary scores as outcomes. Collapsing eight subscales into two scores reduces the number of statistical comparisons, conditional upon empirical support for the factor structure underlying the construction of summary measures (248;365). Some controversy exists regarding the assumption of correlated versus uncorrelated summary measures (366;367). The SF-36 developers maintain that the weighting of the eight subscale scores is constructed to avoid double loading of scores on both the SF-36 physical and mental summary scores, while preserving the highest amount of explained reliable variance of the two second-order constructs. Opponents of this scoring maintain that the physical and mental health dimensions can not be separated, and that this should be reflected in the scoring and interpretation of results. Furthermore, that the current scoring algorithms may lead to spurious findings in cases where extreme opposite levels of physical and mental health subscale scores are present (366;367). This may be a more theoretical issue in the present study: In a non-randomized study comparing on-pump to off-pump CABG, the researchers used correlated physical and mental health summary scores from the RAND-36 questionnaire (368), finding no significant differences between surgical groups as did we in our randomized design with the uncorrelated SF-36 summary scores.
Representation of the variables in the Wilson and Cleary framework

This thesis is only representative of a small selection of the individual (gender, education) and environmental characteristics (quantity and quality of social support) measures that may be subsumed within the Wilson and Cleary pathway model (21). Thus, further interpretation of variance due to the interaction of individual and environmental characteristics was not feasible. Adjustment for preoperative health status appeared to represent the predictive potential of background variables on postoperative health status. The value of our results regarding social support is limited to the role as control variables in the present analyses, in accordance with the results reported by Husak et al (369) who found that the bivariate association of social support to participation in cardiac rehabilitation was insignificant when adjusting for gender, socioeconomic status and comorbidity.

Reliability

Reliability concerns the ability of an instrument to yield consistent results on repeated trials, that is, the degree to which random error is minimized in the instrument (347). The longitudinal design offered a degree of control for potential sources of measurement error during exercise stress testing and cognitive testing. Each individual acted as his/her own control, facilitating interpretation of test results which may be sensitive to limitations from co-morbidity or protocol-specific aspects.

Several strategies were applied to reduce random error, such as pilot testing of the questionnaire, uniform layout of text and response options between instruments in the battery (370), and double-checks of all data entry into the database. In spite of meticulous preparations, administrative errors may happen. We discovered that a single questionnaire was lacking the Hospital Anxiety and Depression Scale, and did first acknowledge this incident at the time of data entry into the database. For all in-patient assessments of patient-reported outcomes, standardized administration of the questionnaire, including debriefing of the respondents (260), was planned in detail prior to inclusion. Where assistance in completing the questionnaire was requested, the method of providing assistance was standardized according to the SF-36 manual (260). The postal assessment at six months after surgery may have been a source of bias due to a different context and time frame, lack of control for participation from significant others during completion of the questionnaire, and the absence of immediate debriefing. However, this assessment was the third of four giving each respondent prior training in the expectations of the questionnaire.
For multi-item instruments, such as the SF-36 and the QOLS-N, internal consistency in this study was comparable to standards from previous validation studies, suggesting that the scales were performing as expected. The performance of single-item questions is more difficult to assess, such as the responses to angina class and overall quality of life. One limitation of this thesis is the absence of a test-retest procedure to assess for consistent responses in our sample on the angina and single-item overall quality of life scales during a period of stable disease activity. We kept track of all written responder comments in the questionnaires for active surveillance of any items with repeated difficulty.

**Conclusions and future perspectives**

**Main conclusions**

1) At one year after CABG, changes in objective functional performance and symptom relief are significant for self-reported health status beyond the predictive ability of preoperative health status, gender or graft patency. Improvement of cardiac capacity and improvement of angina are associated with improved physical health through largely separate paths, when controlling for change in cognitive function. Change in cognitive function is significantly related to self-reported mental health.

2) Cerebral vulnerability, as evidenced by the presence of cerebral ischemic lesions on MRI, is in combination with intraoperative cardiopulmonary bypass associated with less improvement in self-reported physical health at three months after surgery compared to off-pump CABG. This finding needs confirmation in a prospective study.

3) There is no clinically significant difference in angina, health status, or overall quality of life after on- or off-pump coronary artery bypass surgery, measured at three months after surgery or time-averaged over the first year after surgery.

4) Claims of causal associations between general health perceptions and overall quality of life must consider the possibility of bidirectional causal effects.
**Future perspectives**

This study describes the extent and impact of outcomes variation following CABG on health status, controlling for the influence of change in cognitive function. This adds new information to the knowledge base for patient counseling on the expectations of CABG surgery. Clinicians may want to reconsider the use of ‘quality of life’ as an umbrella term in individual patient counseling, and restrict discussions of expectations of CABG to outcomes that are closer to the disease process: symptoms and functioning.

Based on our findings, it is possible that patients may benefit from providing self-assessments of angina and physical functioning pre- and postoperatively, in order to interpret chest pain adequately, discuss the emotional impact of chest pain, and to make the optimal use of physical capacity. Differentiation of non-anginal and anginal chest pain may open up for greater perceived benefit of surgery by reducing self-imposed activity restrictions due to perceived angina.

Current understanding of the experience and meaning of angina is still limited. Instrument development may benefit from further qualitative research. In a quantitative perspective, studies to combine coronary perfusion measurements with patient-reported outcomes will be able to document the association of self-reported physical functioning and angina to an objective variable which may be more specific than angiographic graft patency. Individual differences in the emotional response to anginal pain may be able to explain additional variance in a more comprehensive pain assessment.

When evaluating patient-reported outcomes, the current state of evidence does not suggest a general preference of on-pump versus off-pump surgery. However, evidence of cerebral arteriosclerotic disease may be a risk factor to consider over chronological age, if off-pump CABG is an available option for revascularization.

Overall quality of life perceptions should be assessed in clinical trials and longitudinal research in order to be documented and statistically modeled. Study designs should include a sample size and appropriate analytical methods to allow for bidirectional causality when concepts at a high level of integration and abstraction are considered. Researchers should assess the comparability of groups regarding overall quality of life. If not equal, then attempts to statistically adjust may be implemented, with explicit assumptions of the role allocated to this variable.
To allow for methodological critique and comparison across studies, the complexity of design and analysis of patient-reported outcomes data indicates full disclosure of longitudinal results and analytical strategy. This may be practically impossible to accomplish in summary papers where patient-reported outcomes often are secondary outcomes. An alternative is on-line access to supplementary material, which eases the burden of multiple publications from the same data set. As this places the researcher at a disadvantage in terms of credit for work, the alternative of separate publication of patient-reported outcomes data may be preferable. Regardless of the channel, adherence to guidelines for the reporting of patient-reported outcomes may preserve the integrity and promote development of this field of research.

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Errata

p.2, third paragraph, line 2: .....becomes....

p.5: Text added below Figure 1, two lines stating copyright and permission to reproduce.

p.10, second paragraph: Emotional responses and adaptations to experiences of angina differ: some patients may plan to avoid angina and assume a more sedentary lifestyle, while others may adopt activities that confront the threshold for angina and pursue a more active lifestyle..

p.15, second paragraph, line 3: Oslo University Hospital, Rikshospitalet.

p.18, third paragraph, line 5: Rey Auditory Verbal Learning Test (RAVLT)

p.21, second paragraph, line 8: rheumatoid arthritis and systemic lupus erythematosus to replace the abbreviations RA and SLE.

p.38, third paragraph, line 4: “Finally, the conditions....” to replace “Finally, and the conditions...”.

p.53, citation 71: The correct abbreviation for this journal is J Health Soc Behav.

p.54, citation 79: “....report by the European Coronary Surgery Study Group.

p.68, citation 222: Second author’s name corrected to Meriläinen.
Paper I
Change in cardiac and cognitive function, and self-reported outcomes at one year after coronary artery bypass surgery.

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Abstract

Objectives
Although health status after coronary artery bypass surgery improves at the group level, individual outcomes demonstrate a large range of variation. We aimed to evaluate the relative importance of change in cardiac and cognitive function together with symptom status, for physical and mental health at one year after coronary artery bypass surgery.

Methods
The outcomes in a multivariable regression analysis (n=86) were self-reported physical and mental health (Short Form 36) at 12 months’ follow-up, adjusting for baseline. Independent variables were change in exercise capacity (staged ergometer protocol), cognitive function (neurocognitive test battery), and self-reported improvement of angina. Graft patency was evaluated by angiography in 82 of 86 patients.

Results
Following surgery, health status was comparable to the age- and gender matched population norm. Improvement of angina was associated with a gain in physical health in the range of half a standard deviation (β 0.23, p=0.012). Change in observed physical exercise capacity (mean 199 Wmin, sd 426) accounted for 9% of the variance in physical health (β 0.42, p=0.001). A positive change in cognitive function was significantly related to mental health (β 0.52, p=0.007), but not physical health. Graft occlusion (22 of 82 patients), was not significant for health status.

Conclusions
Individual variation in objective functional performance and symptom relief is significant for self-reported health status, beyond the predictive ability of preoperative health status, gender or graft patency. Awareness of the extent and impact of outcomes variation is important when counseling patients on the expectations of coronary artery bypass surgery.
Ultramini-abstract

Individual changes in cardiac performance, cognitive function and angina, assessed one year after surgery, were significant for subjective health status relative to the predictions possible from preoperative health status, gender or graft patency. Awareness of the extent and impact of outcomes variation on health status is important when counseling patients.
**Introduction**

Coronary artery bypass grafting (CABG) aims to reduce the burden of ischemic heart disease by prolonging survival, relieving angina pectoris, and improving on the health-related quality of life (1). A possible causal path suggests that successful revascularization to improve coronary flow reserve is followed by an improvement in cardiac work capacity, symptoms, and self-reported health status, where personal and environmental characteristics may influence each level of outcomes (2). Previous research supports that health status improves at the group level after coronary artery bypass surgery, although much variation between individuals has been documented regarding objective measures of clinical outcome as well as self-reported symptoms and health status (3-5). Thus, while the patients as a group share a clinically significant benefit of surgery, the degree of benefit is not uniform and in fact, some patients experience a decline (5;6).

The impact of change in physiological function as it relates to change in self-reported outcomes is not well understood. Cross-sectional studies that combine objective and self-reported variables do not account for individual change following CABG (7;8). Longitudinal studies are rare and focus either cardiac function (9) or cognitive function (10;11) in relation to self-reported variables, but not the combination of these aspects. It is of particular interest to evaluate the importance of change in cognitive function in combination with cardiac function and symptom relief, as CABG has been associated with intra- and postoperative neurological injury, ranging from stroke through transient confusion to subclinical cognitive decline (12). Thus, the aim of this study was to investigate the relative importance of change in objectively measured cardiac and cognitive function together with symptom status, for self-reported health status at one year after coronary artery bypass surgery.

**Materials and methods**

**Patient sample and procedure**

The patient sample for this planned, longitudinal analysis came from a clinical study of CABG surgery performed on-pump or off-pump. Pre- and postoperative assessments took place at a
single facility with standardized procedures for collection and interpretation of data. The parent study included 120 patients, aged 40-80 years, with stable angina and moderate to good left ventricular function. The study protocol was approved by the Regional Ethics Committee, and patients provided written and informed consent. Details of the surgical procedure have been reported elsewhere (13;14). We have previously reported on the association of preoperative cerebral ischemic lesions to health status at three months after CABG (15), and on bidirectional relationships between overall life satisfaction and general health perceptions (16).

Patients were recruited for the study at the time of preoperative angiography. Cardiac and cognitive testing was performed after admission for surgery, one to four days preoperatively. All in-patient assessments of self-reported data were scheduled before any further clinical or research diagnostics. Initial flowmetric control for graft quality was performed during surgery, followed by coronary angiography after closure of the sternum/chest to ensure that all patients were left with the optimum technical result (13).

Individual characteristics at baseline included age, gender, education, comorbidity (diabetes, asthma, rheumatoid arthritis, hypertension or other). Environmental characteristics were measured as co-habitation versus living alone, perceived quality of social support, and centrality of residence to indicate access to health care services.

In addition to preoperative data collection, follow-up assessments were completed for cardiac function / exercise stress testing (12 months), cognitive function (3 and 12 months after surgery), and self-reported outcomes (3, 6 and 12 months). Thus, complete sets of observed and self-reported data were available from two time-points; baseline and 12 months’ follow-up. Complete sets of objective and subjective data for this analysis were available for 86 of 120 patients enrolled in the main study (71.7%). At 12 months after surgery, 82 of 86 patients in this sample underwent a follow-up angiography to determine graft patency.

During the study period, early mortality (2 patients) and withdrawal (3 patients) left 115 out of 120 patients eligible for follow-up. Both pre and postoperative stress testing were performed in 99 patients. Six patients refused follow-up testing of cognitive function, two were not tested for other reasons. Three patients were lacking in one or more subscales of the SF-36, precluding
calculation of SF-36 Physical and Mental health component scales. Six patients, five at baseline and one at follow-up, were unable to grade their angina on the CCS scale.

**Observed functional status**
Change in cardiac function was measured as change in observed maximum physical exercise work capacity in Watt minutes. On an ergometer bicycle and according to standardized protocol, entry level resistance of 50 Watt was followed by an incremental increase of 50 Watt for every six minutes of exercise completed (17). Testing was limited by exhaustion, angina, or persistent ST-segment changes of ≥ 1 mm below baseline recording.

A detailed assessment of cognitive function was performed with a test battery including assessment of six neuropsychological components; motor co-ordination, psychomotor speed, attention, verbal learning and delayed recall, verbal abstraction and fluency, and visuoconstructive abilities, comprising a total of 10 measures (18). Preoperative scores for each test were standardized to yield z-scores (sum score minus the group mean score, divided by the standard deviation) and combined to a single sum score for each individual. At 12 months’ follow-up, the individual test scores were z-transformed relative to the preoperative mean and standard deviation. The use of continuous z-scores reflected individual change in the direction of a decline (lower score) or improvement (a higher score than baseline test results).

**Self-reported variables**
Self-reported data were angina and health status. Angina was assessed on the ordinal level Canadian Cardiovascular Society scale (19). The 36-item Medical Outcomes Study Short Form 36 (SF-36) reflects health status during the past four weeks. Two summary scores, physical and mental health, are calculated from eight subscales, ranging from zero to 100 with higher scores indicating better health. (20). We report norm-based SF-36 Physical and Mental health component scores that compare to an age and gender matched national reference population with a mean of 50 and a standard deviation of 10. SF-36 subscales loading most heavily on the mental component include vitality, emotional role functioning, social functioning and mental health. The physical component represents physical functioning, physical role functioning, bodily pain and general health.
Statistical analyses
Characteristics of patients included and excluded in the analysis were assessed using non-parametric ($\chi^2$, Fisher’s exact test, Mann-Whitney) and parametric (Student’s t) tests for independent samples. Use of cardiopulmonary bypass was recorded as actual use, regardless of the randomization in the parent study. Patients who had undergone coronary reintervention since surgery were included in the analysis, as these patients were managed according to the current standard of practice. The level of statistical significance was set at alpha=0.05. Change in the norm-referenced SF-36 summary scores of half a standard deviation, usually corresponding to 5 points, is currently regarded as a conservative estimate of clinical significance, while smaller differences may represent a difference that would be perceived as beneficial by the patient or lead to a change in treatment (21). Data management and analysis were handled with the SPSS version 15.0 (SPSS Inc., Chicago IL).

Initial analysis examined associations amongst the predictor variables and the eight SF-36 subscales (20). Bivariate correlations of change in cognitive and cardiac function to the SF-36 subscales were analyzed with change scores, calculated by subtracting the baseline score from the follow-up score; a positive number indicating improvement and a negative number indicating a decline. The ordinal level angina scale was dichotomized to represent improvement versus no change or worsening of angina compared to preoperative status.

In two hierarchical regression models, we evaluated the combined influence of change in cardiac function, cognitive function, and symptom relief on self-reported physical and mental health at follow-up, adjusting for gender, preoperative health status, cardiac and cognitive function in all models. To be able to compare the standardized regression (beta) coefficients, change was evaluated by entering the 1-year total scores, rather than change scores, with adjustment for preoperative scores. The analysis was guided by the Wilson and Cleary causal pathway model (2). Objective functional tests represented bio-physiological variables, believed to influence symptom status and self-reported health status (functioning and general health perceptions). Two-way interactions were tested for angina status, change in observed exercise capacity, and gender. The number of covariates was limited to one per 10 respondents. Stability of the final models were tested with potential covariates, specifically including on-versus off-pump procedure, graft patency at 12 months, coronary reintervention, comorbidity (previous...
myocardial infarction, preoperative obstructive lung disease, diabetes), age, education, co-habitation versus living alone, perceived quality of social support, centrality of residence.

Results

Preoperative assessment
The patient sample is characterized in Table 1. The SF-36 Physical and Mental health scores were comparable between those included in the analysis versus patients excluded due to the lack of complete sets of data. Differences were noted for cognitive function scores, the proportion of off-pump procedures, female gender, and patients reporting more than one comorbidity, with subsequent adjustments in later multivariable analyses. Before surgery, SF-36 Physical and Mental health scores were significantly lower than in the observed normative population mean of 50 points: -7.6 and -7.3 points respectively (one-sample t-test, p<0.001). Preoperative cognitive function was comparable to age-group norms, with exception of marginally lower memory scores (data not shown). Preoperative observed physical exercise capacity correlated with SF-36 Physical health (r=0.34, p=0.001) and self-reported angina / CCS class (r=-0.26, p=0.017, n=82), while cognitive function correlated with SF-36 Mental health (r=0.35, p=0.001).

Objective evaluations at 12 months after CABG
The mean improvement in observed physical exercise capacity was 199 Wmin (sd 426, paired t-test p<0.001). Cognitive function scores improved overall by z=0.25 (sd 0.32, paired t-test p<0.001) with a strong test-retest correlation (r=0.86, p<0.001).

Six patients had undergone coronary reintervention since CABG; five of these to previously grafted coronary arteries. One patient had recovered completely at three months after surgery from a mild postoperative stroke. Follow-up angiograms revealed that 21 of 82 patients had a single graft without detectable flow, while one patient had three occluded grafts.

Subjective evaluations at 12 months after CABG
Sixty-four patients (74.4%) reported improvement of angina. Sixty-three patients (73.3%) reported no angina at follow-up. Table 2 displays the corresponding SF-36 subscale change
scores with correlation coefficients to change in cardiac function, cognitive function, and symptom relief. Change in physical exercise capacity was associated with self-reported physical functioning, bodily pain and physical role limitations. Change in cognitive function demonstrated minor correlation coefficients to social functioning, vitality and physical functioning. Symptom relief was primarily associated with bodily pain and physical role limitations.

As a group, the mean change in SF-36 Physical and Mental health scores was clinically significant, resulting in SF-36 Physical and Mental health scores that improved from below to within the population mean before surgery at follow-up (95% confidence interval, Physical health 48.3 to 52.0 points; Mental health 46.7 to 50.4 points). The correlation coefficients between SF-36 Physical and Mental health, were $r= -0.17$ ($p=0.108$) at baseline, $r= 0.15$ ($p=0.163$) at 12 months after surgery, and between change scores $r= -0.13$ ($p=0.219$).

Regression analyses of subjective physical and mental health

The initial regression models included gender and preoperative self-reported health status, which together explained 17.0% of the variance (adjusted $R^2$) in SF-36 Physical health scores and 18.2% of the variance in SF-36 Mental health scores at one year after CABG. After adding all planned independent variables (Table 3), the analysis demonstrated that improvement of angina and change in observed physical exercise capacity were significantly associated with change in SF-36 Physical health. Improved angina class was associated with an improvement in physical health of 4.7 points, independently accounting for 5.1% of the total variance. The mean improvement in exercise capacity was associated with 1.2 points increase in SF-36 Physical health, accounting for 9% of the variance. These findings seemed predominantly to represent independent effects. Change in exercise capacity, improvement of angina, or gender did not show significant interaction effects on SF-36 Physical or Mental health scores. Change in SF-36 Mental health scores was associated with change in cognitive function; half a standard deviation decline in cognitive function corresponded to a 3.7 point decline in mental health.

The regression models were stable when individually adding possible confounders, identified through bivariate analysis or clinical judgment. Preoperative obstructive lung disease ($\Delta R^2 4.7\%, p=0.014$), and >1 self-reported comorbidity ($\Delta R^2 2.9\%, p=0.054$) added explained
variance to the physical health model without major alterations in the other predictors. No control variables showed significant effects in the mental health regression model. The final regression models explained 33% of the variance in SF-36 Physical health scores, and 27% of the variance in SF-36 Mental health scores at one year after CABG surgery.

Two follow-up analyses were run to evaluate the influence of graft patency or multivariable outliers. The presence of an occluded graft was not significant for SF-36 Physical health (df 81, β 0.02, p=0.807) or SF-36 Mental health (df 81, β 0.13, p=0.204). Two multivariable outliers were identified in the mental health model. Exclusion of these outliers increased the explanatory value of the model (ΔR² 3%) without altering the main effect associated with change in cognitive function.

Discussion

There are two key findings in our study of change in physical and mental health at one year after CABG surgery. The first is that the combined influence of symptom relief, change in observed physical exercise capacity and change in cognitive function, reveals significant and unique associations to change in physical and mental health. The physiological and symptomatic variation in outcomes is statistically beyond what can be predicted from preoperative health status or gender, the difference is clinically relevant, and the presence of graft occlusion per se does not appear to be of importance for this variation in self-reported outcomes. The extent and impact of outcomes variation is relevant when counseling patients on their expectations of surgery. The second key finding is that change in cognitive function, while being predictive of mental health, is not significant for physical health. This study suggests that change in physical health may be interpreted independently of cognitive functioning.

The primary aim of coronary artery bypass surgery is to prolong life, and secondly to reduce angina and improve health status (1). A concept of successful surgery may cover multiple related elements such as patent coronary grafts, relief of angina, objectively measured functional improvement, the absence of complications such as adverse neurological outcomes, and improved health status as experienced by the patient. At the group level, this patient sample
demonstrated an expected benefit of surgery, increasing SF-36 Physical and Mental health scores to within the age- and gender-matched population norm. Our results are consistent with previous studies in that the experience of symptom relief varies; one in five patients with preoperative symptoms will still report exertional angina at one year after surgery (22).

We observed a mean improvement in exercise capacity of 25% relative to preoperative status. Cross-sectional studies regarding the correlation of exercise capacity to self-reported physical health are in line with our findings (7;23). However, previous longitudinal studies combining objective and self-reported outcomes after CABG are rare, report weaker correlations to change in exercise capacity, and lack control for cognitive function (7;9). The latter variable is important in light of reports that suggest a causal association of cognitive function to self-reported physical health (10;24), results that were not replicated in the present study. We noted a modest bivariate association between change in cognitive function and the SF-36 subscale Physical functioning (Table 2). Cognitive functioning may play a role in patients’ ability to gain a maximum health benefit during rehabilitation (8;24). However, we suggest that cognitive function may also be interpreted as representing an underlying causal variable. Single organ indicators of a multi-organ disease may share an association to the underlying disease process – atherosclerosis – and show up as significant predictors on a broad spectrum of outcomes, including self-reported health status after CABG. In line with this interpretation, Ho and co-workers established noncoronary manifestations of atherosclerosis as predictive of cognitive decline after CABG (25). It is notable that our patient sample was representative of those with moderate to good left ventricular function. Other patients, with less well preserved left ventricular function, may demonstrate known but still not fully understood correlations between physical and cognitive indicators (26). We observed a trend towards improvement in cognitive function scores from baseline for 74% of the patients, probably reflective of a learning effect as a result of testing (27). As this analysis was not by intention-to-treat but controlled for the actual use of cardiopulmonary bypass, the results do not inform on the off-pump versus on-pump controversy. However, cognitive function at one year after the procedure was not indicative of a general decline. Although patients with coronary artery disease may demonstrate more cognitive impairment than heart-healthy controls, studies within the last decade using a
control group suggest little postoperative change in cognitive function that is attributable to CABG surgery (27;28).

The presence of occluded grafts was not significant for self-reported health status, a finding that was unrelated to the number of distal anastomoses created at surgery. Furthermore, graft occlusion did not correlate significantly with change in observed physical exercise capacity (data not shown). Providing that sufficient global improvement in coronary flow reserve has been achieved, a coronary graft may occlude without objective evidence of ischemia, usually due to adequate collateral or competing circulation. In other cases, an occluded graft may lead to silent ischemia without angina. Two issues complicate comparison across studies. First, previous studies demonstrate a wide range of completeness of follow-up angiography of patients included or randomized. The less complete follow-up, the greater the potential for a relative oversampling of patients with symptomatic graft occlusion leading to angiographic evaluation. Secondly, a pathological graft may be defined as the absence of flow, as in this study, or as a stenosis greater than 50% or 75% of the vessel diameter. The wider definition will cover a greater proportion of a patient sample and increase the probability of identifying a statistical association, although no additional argument for clinical relevance is implied.

Several features and limitations of this study should be acknowledged. Pre- and postoperative standardization and protocol adherence was enhanced by a single-center design. Although our patient sample was of moderate size, the surgical results and graft patency rates were comparable to larger studies after on- or off-pump procedures (29). All of our regression models adjusted for baseline health status, providing statistical adjustment for scaling effects and the tendency for extreme scores to be followed by less deviation from the mean (regression to the mean). Patient-reported outcomes add to our understanding of the impact of illness and treatment. However, the interpretation of patient-reported outcomes may be complicated by selective reporting or the recalibration of respondents’ internal values (30). This study did not allow for quantification of such effects. Baseline and follow-up medication was not entered into the analysis. Missing data, in particular for observed physical exercise capacity, suggests a potential for sampling bias. However, a comparison between patients included versus excluded in our analysis did not demonstrate a difference in health status at follow-up. We also performed a sensitivity analysis of the impact of missing physical exercise test data which
confirmed our overall findings, by first imputing the 12.5 percentile (low end) for all missing pre- and postoperative results of physical exercise capacity (n=104), and then repeating the procedure using the 87.5 percentile (high end). Use of a theoretical causal pathway model to guide the analysis strengthens this study. We acknowledge the possibility of bidirectional causal effects within a chain of self-reported outcomes (2), although we have previously found this to be evident at other time-points then at one year after CABG regarding the relationship between the SF-36 general health subscale and overall quality of life (16).

Summing up at one year after coronary artery surgery, changes in objective functional performance and symptom relief are significant for self-reported health status beyond the predictive ability of preoperative health status, gender or graft patency. Symptom relief and change in observed physical exercise capacity is significant for self-reported physical health, independent of cognitive function. A positive change in cognitive function is significantly related to self-reported mental health. Awareness of the extent and impact of outcomes variation on health status is important when counseling patients on the expectations of CABG surgery.

**Acknowledgements**

The authors thank the respondents for sharing their experiences, and Torbjørn Moum PhD for statistical advice. The staff at the Interventional Centre and the Department of Thoracic and Cardiovascular Surgery is acknowledged for skilful and compassionate patient care. Anonymous data for the population reference norms used in this study are from the Health Status Survey 2002, provided by The Norwegian Social Science Data Services (NSD), with data collection and organization conducted by Statistics Norway. Neither Statistics Norway nor NSD are responsible for the analyses or interpretations put forth in this paper.
Table 1 Preoperative and procedural characteristics of the patient sample

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Included n = 86</th>
<th>Excluded n = 34</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
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<td>Male : female</td>
<td>74 : 12</td>
<td>20 : 14</td>
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<tr>
<td>Age, years</td>
<td>64.0 (8.0)</td>
<td>65.7 (8.0)</td>
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<tr>
<td>Education, years</td>
<td>10.5 (3.0)</td>
<td>9.9 (2.8)</td>
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<tr>
<td>Living alone</td>
<td>15 (17.4%)</td>
<td>3 (8.8%)</td>
<td>0.273 ‡</td>
</tr>
<tr>
<td>Physical exercise capacity, Watt*min (n=104)</td>
<td>794 (449)</td>
<td>762 (420)</td>
<td>0.783</td>
</tr>
<tr>
<td>Cognitive function, z-score (n=118)</td>
<td>0.09 (0.56)</td>
<td>-0.20 (0.64)</td>
<td>0.019</td>
</tr>
<tr>
<td>Number of vessels with significant stenosis</td>
<td></td>
<td></td>
<td>0.951 †</td>
</tr>
<tr>
<td>3 or left main</td>
<td>45 (52.3%)</td>
<td>17 (50.0%)</td>
<td></td>
</tr>
<tr>
<td>1-2</td>
<td>41 (47.7%)</td>
<td>17 (50.0%)</td>
<td></td>
</tr>
<tr>
<td>Ejection fraction, % (n=117)</td>
<td>70 (11)</td>
<td>73 (11)</td>
<td>0.186</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>43 (50.0%)</td>
<td>12 (35.3%)</td>
<td>0.160 ‡</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>12 (14.0%)</td>
<td>3 (8.8%)</td>
<td>0.552 ‡</td>
</tr>
<tr>
<td>Stroke or transitory ischemic attack</td>
<td>6 (7.0%)</td>
<td>3 (8.8%)</td>
<td>0.712 ‡</td>
</tr>
<tr>
<td>Diabetes</td>
<td>11 (12.8%)</td>
<td>9 (26.5%)</td>
<td>0.101 ‡</td>
</tr>
<tr>
<td>Hypertension</td>
<td>32 (37.2%)</td>
<td>19 (55.9%)</td>
<td>0.069 ‡</td>
</tr>
</tbody>
</table>

Self-reported data:

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Included n = 86</th>
<th>Excluded n = 34</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No angina</td>
<td>9 (10.5%)</td>
<td>1 (2.9%)</td>
<td>.279 ‡</td>
</tr>
<tr>
<td>CCS class III or IV (n=115)</td>
<td>20 (24.4%)</td>
<td>13 (39.4%)</td>
<td>.117 ‡</td>
</tr>
<tr>
<td>&gt;1 comorbidity</td>
<td>16 (18.6%)</td>
<td>13 (38.2%)</td>
<td>.033 ‡</td>
</tr>
<tr>
<td>SF-36 Physical health (n=118)</td>
<td>42.4 (8.4)</td>
<td>40.2 (8.2)</td>
<td>.196</td>
</tr>
<tr>
<td>SF-36 Mental health (n=118)</td>
<td>42.7 (11.5)</td>
<td>43.2 (11.5)</td>
<td>.819</td>
</tr>
</tbody>
</table>

Procedural characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Included n = 86</th>
<th>Excluded n = 34</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of distal anastomoses</td>
<td>2.7 (.9)</td>
<td>2.5 (1.0)</td>
<td>0.283 ‡</td>
</tr>
<tr>
<td>Total duration of surgery, minutes</td>
<td>175 (51)</td>
<td>181 (59)</td>
<td>0.637</td>
</tr>
<tr>
<td>Off-pump procedure</td>
<td>44 (51.2%)</td>
<td>9 (26.5%)</td>
<td>0.015 ‡</td>
</tr>
</tbody>
</table>
Values are presented as mean (standard deviation) or counts (%).
The p-values refer to Student’s t-test or
† Mann-Whitney U for continuous variables;
‡ chi-square test or
§ Fisher’s exact test for categorical values.

Legend:
CCS  Canadian Cardiovascular Society angina scale.
SF-36  Medical Outcomes Study, Short Form 36.
Table 2  Health status, change scores at one year after CABG with bivariate correlations to predictor variables.

<table>
<thead>
<tr>
<th>SF36 subscales</th>
<th>Mean change (sd)</th>
<th>Δ Physical exercise capacity</th>
<th>Δ Neuro-cognitive function</th>
<th>Angina, improved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical functioning</td>
<td>19.2 (23.2)</td>
<td>.25 *</td>
<td>.12</td>
<td>.11</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>21.4 (31.4)</td>
<td>.32 †</td>
<td>.06</td>
<td>.31 †</td>
</tr>
<tr>
<td>Role, physical</td>
<td>35.2 (46.2)</td>
<td>.23 *</td>
<td>-.06</td>
<td>.29 *</td>
</tr>
<tr>
<td>General health</td>
<td>9.1 (19.5)</td>
<td>.01</td>
<td>.07</td>
<td>.03</td>
</tr>
<tr>
<td>Vitality</td>
<td>14.0 (21.2)</td>
<td>.07</td>
<td>.10</td>
<td>.14</td>
</tr>
<tr>
<td>Social functioning</td>
<td>14.2 (22.4)</td>
<td>.05</td>
<td>.19</td>
<td>.03</td>
</tr>
<tr>
<td>Role, emotional</td>
<td>29.1 (49.0)</td>
<td>.02</td>
<td>.15</td>
<td>-.02</td>
</tr>
<tr>
<td>Mental health</td>
<td>8.7 (14.8)</td>
<td>-.04</td>
<td>.07</td>
<td>-.03</td>
</tr>
</tbody>
</table>

SF36 summary scores

<table>
<thead>
<tr>
<th></th>
<th>Mean change (sd)</th>
<th>Δ Physical exercise capacity</th>
<th>Δ Neuro-cognitive function</th>
<th>Angina, improved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical health</td>
<td>7.8 (9.1) ‡</td>
<td>.37 ‡</td>
<td>.02</td>
<td>.33 ‡</td>
</tr>
<tr>
<td>Mental health</td>
<td>5.8 (10.9) ‡</td>
<td>-.10</td>
<td>.16</td>
<td>-.08</td>
</tr>
</tbody>
</table>

N = 86. All correlation coefficients are Pearson’s r.

Change scores are relative to preoperative scores; a positive change indicates improvement. The scale is 0-100.

Legend

*  p<0.05
†  p<0.01
‡  Paired t-test comparing preoperative to one year after surgery: p<0.001
Table 3  Multivariable models of physical and mental health at 1 year after coronary artery bypass surgery

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>SF-36 Physical health</th>
<th>SF-36 Mental health</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β</td>
<td>p-value</td>
</tr>
<tr>
<td>Observed physical exercise capacity at 1 year after CABG</td>
<td>0.42</td>
<td>0.001</td>
</tr>
<tr>
<td>Preoperative observed physical exercise capacity</td>
<td>-0.37</td>
<td>0.005</td>
</tr>
<tr>
<td>Cognitive function at 1 year after CABG</td>
<td>0.28</td>
<td>0.120</td>
</tr>
<tr>
<td>Preoperative cognitive function</td>
<td>-0.33</td>
<td>0.065</td>
</tr>
<tr>
<td>Improvement of angina</td>
<td>0.23</td>
<td>0.012</td>
</tr>
<tr>
<td>Gender (female coded 1)</td>
<td>-0.06</td>
<td>0.530</td>
</tr>
<tr>
<td>Preoperative SF-36 Physical / Mental health score</td>
<td>0.44</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

R square 0.39  Adjusted R square 0.33
R square 0.33  Adjusted R square 0.27

Legend

β values are the standardized regression coefficients indicating the relative strength of association between the independent variables.
References


Paper II
Preoperative cerebral ischemic lesions predict physical health status after on-pump coronary artery bypass surgery

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Background: Risk assessment is integral to patient selection and counseling before coronary artery revascularization. We studied the predictive ability of cerebral magnetic resonance imaging of preoperative and postoperative cerebral ischemic injury on self-reported physical and mental health at 3 months after coronary artery bypass surgery with or without use of cardiopulmonary bypass.

Methods: In a prospective clinical trial comparing on-pump and off-pump surgery, 120 patients responded to a questionnaire for self-report of angina (Canadian Cardiovascular Society scale) and physical and mental health status (Short Form 36) at baseline before preoperative cerebral magnetic resonance imaging. Preoperative sets of both magnetic resonance imaging and self-assessments were available for 103 (85.8%) patients. These patients were grouped according to classification of preoperative cerebral magnetic resonance imaging findings. Analysis of covariance determined the association of (1) preoperative magnetic resonance imaging status, (2) new postoperative cerebral lesions, and (3) actual use of cardiopulmonary bypass to physical and mental health.

Results: At 3 months after surgical intervention, 98 of 103 patients completed follow-up. The analysis revealed an interaction effect of preoperative cerebral ischemic injury and use of cardiopulmonary bypass on physical health ($F_{11005}=9.07$, $P=.003$) independent of age. No independent effects on health status were found of baseline magnetic resonance imaging or new cerebral lesions at 3 months.

Conclusions: This study strongly suggests that the combination of preoperative cerebral ischemic injury and use of cardiopulmonary bypass can predict postoperative health status at 3 months. Cerebral magnetic resonance imaging might be a more specific indicator than age for preoperative assessment of vulnerability or resilience during rehabilitation after on-pump cardiac surgery.

Patient-reported outcomes, the subjective and multidimensional assessments of the effect of disease and its treatment, remain essential to understand and compare the processes and outcomes of health care. The association between self-reported health status and the neurologic effect of cardiac surgery is not fully understood, possibly because prior research in this field has focused on the relationship between subjective and objective measures of health rather than correlation to their common causal indicators, such as signs of cerebral injury visualized by means of cerebral magnetic resonance imaging (MRI).

Subclinical cerebrovascular disease is prevalent in the adult population and even more so in the patient population with coronary arteriosclerosis. Epidemiologic research reports 15.3% overall prevalence of infarct-like lesions on cerebral MRI in the 55- to 72-year age group, 10 times the prevalence of stroke. In the population older than 65 years, frail health has been shown to correlate with infarct-like lesions,
as well as cardiovascular disease. A study of 15 patients undergoing coronary artery bypass revealed that 14 had preoperative MRI abnormalities, with 4 patients showing new cerebral lesions after the operation. Others have reported from 21% to 45% presence of acute postoperative cerebral lesions on MRI without overt clinical signs of neurologic deficit. However, patient-reported outcomes have, to our knowledge, not been published in relation to MRI findings in this patient population. For the present study, we planned a secondary analysis of data from a clinical trial of 120 patients undergoing off-pump versus conventional on-pump coronary artery bypass surgery. Previously reported conclusions from this trial include similar perioperative outcomes and 3-month graft patency rates and higher counts of intraoperative cerebral emboli in on-pump patients.

Given the prevalence of subclinical cerebrovascular disease and theory suggesting a causal pathway from clinical variables to self-reported health status, the purpose of the present study was to assess the predictive ability of preoperative and postoperative cerebral MRI findings on physical and mental health reported by patients at 3 months after surgery. We hypothesized a priori that evidence of cerebral ischemic injury would identify patients at higher risk and that new postoperative cerebral lesions or the use of intraoperative cardiopulmonary bypass would modify outcomes.

**Patients and Methods**

**Sample**

Data stem from a clinical trial in which 120 patients aged between 40 and 80 years with stable angina pectoris were randomized to elective on- or off-pump coronary artery bypass surgery. Exclusion criteria were a left ventricular ejection fraction of less than 30%, a serum creatinine level of greater than 200 mmol/L, and lack of ability to read, write, or communicate verbally in Norwegian. In the present study the analysis was based on available patients completing the combination of cerebral MRI and self-reported health status assessments before surgical intervention and at 3 months postoperatively.

**Procedure**

The study protocol was approved by the regional ethics committee. After providing written and informed consent, the patients responded to a health status questionnaire administered by one of the authors. The procedure for all self-assessments was standardized and scheduled before further diagnostics (including clinical neurologic and cerebral MRI examination), before the operation, and at 3 months after the operation.

The diagnostic and surgical procedures, including management of anesthesia and cardiopulmonary bypass, have earlier been described in detail. Briefly summarized, all operations were performed after achievement of balanced opiate, barbiturate, and inhalation anesthesia. The internal thoracic artery was used for revascularization of the left anterior descending coronary artery, and saphenous vein grafts were used for all other vessels. The distal anastomoses were performed first, and the proximal anastomoses were performed successively thereafter with a partial aortic clamp. On-table graft angiography was performed, followed by graft revision if questionable quality of the anastomosis or the graft was revealed.

In the on-pump group the bypass circuit was tip-to-tip heparin coated with the Duraflo II heparin surface (Bentley/Baxter, Uden, the Netherlands), and activated coagulation time was maintained at greater than 480 seconds. All operations were performed with moderate general hypothermia (28°C-32°C) and cold St Thomas antegrade cardioplegic solution. Bypass management included membrane oxygenators, arterial line filters, use of a roller pump and cardiotomy suction, nonpulsatile flow of 2.4 L/min per square meter, and a target mean arterial pressure of greater than 50 mm Hg.

In the beating-heart patients heparin (1 mg/kg) was administered during takedown of the internal thoracic artery, and activated coagulation time was maintained at greater than 250 seconds. The distal anastomoses were performed with the use of snare (Gore Tex 3-0; W.L.Gore & Associates, Flagstaff, Ariz) and stabilizers (Octopus I and II, Medtronic, Minneapolis, Minn) combined with deep pericardial retraction sutures and, as needed, an apical suction device (Starfish; Medtronic, Minneapolis, Minn). A carbon dioxide blower (Ethicon Cardiovations, Summerville, NJ) was used to obtain a bloodless anastomosis field.

**Variables**

**Physical and mental health.** The 36-item Medical Outcomes Study Short Form 36 (SF-36) reflects health status during the past 4 weeks. Two summary scores, physical and mental health, are calculated from 8 subscales ranging from 0 to 100, with higher scores indicating better health. After standardization and linear transformation, the summary scores compare with a population reference mean of 50 and a standard deviation of 10, so that each point on the scale represents one tenth of a standard deviation. SF-36 subscales loading most heavily on the mental component include vitality, emotional role functioning, social functioning, and mental health. The physical component represents physical functioning, physical role functioning, bodily pain, and general health.

**MRI.** Cerebral MRI was performed with a 1.5-T scanner with axial proton-density and T2-weighted turbospin-echo/echocardiography with 5-mm slice thickness and 1.5-mm slice intergap. The repetition time was 2200 ms, and the echocardiographic time was 14 ms for proton and 85 ms for T2. The images were evaluated by an experienced neuroradiologist blinded to the patients' clinical status and use of cardiopulmonary bypass. The presence of preoperative cerebral ischemic lesions was scored as absent, borderline (<5 mm), or pathologic (≥5 mm). At 3 months' follow-up MRI, new lesions were defined as one or more new cerebral lesions larger than 2 mm that were not present at the preoperative examination.
Intraoperative and immediate postoperative events. Patients converted from off-pump surgery to use of cardiopulmonary bypass, either because of hemodynamic instability or for technical reasons, were identified by using a dichotomous variable. Manual anesthesia records were reviewed to determine preanesthetic and intraoperative systolic blood pressure, use of inotropes beyond routine administration, intraoperative events, and, if applicable, mean arterial pressure during cardiopulmonary bypass. Intensive care flowcharts were reviewed to identify the use of intra-aortic balloon pumping or incidents of mean arterial blood pressure of less than 60 mm Hg on the day of the operation.

Postoperative course. Dichotomous variables were entered for atrial fibrillation, pulmonary complications, and leg or chest wound infection, with data collected from physician notes at the planned in-patient follow-up. Patients’ comments on questionnaires and field notes during interviews were screened for any persisting problems not covered in the self-assessment questionnaire, where pain, sleep quality, and sexual difficulties were queried. The number of significant life events since the operation was assessed by 8 items representing stressors, such as the loss of a spouse.

Angina. The Canadian Cardiovascular Society scale was used for self-report. Scores at 3 months were dichotomized by comparison with baseline level to determine improvement versus no improvement or worsening of angina.

Statistical Analysis
The SF-36 scoring manuals directed handling of missing items and subscale and summary score calculations. The Norwegian National Health Survey of 2002 provided population reference values for norm-based scoring weighted for age and sex to match the sample.

Patient-reported outcomes on the basis of randomization to the on- or off-pump procedure (intention-to-treat analysis) have previously been reported. For purposes of the present study, use of cardiopulmonary bypass was defined as actual use regardless of randomization; a patient crossing over from off- to on-pump surgery was classified in the on-pump group, and the influence of conversion was examined during analysis.

After visual inspection of health status box plots, patients with borderline and pathologic MRI findings were clustered, leaving patients with normal MRI results at baseline to constitute a group expected to prove resilient to the burden of surgical intervention. The a priori hypotheses were tested in covariance models, where we included sex and improvement of angina as factors and baseline health status as a linear covariate, with additional postoperative factors if the P value of bivariate correlation to 3 months’ health status was less than .05. As we expected the correlation of health status as a linear covariate, with additional postoperative factors, the final covariance models were challenged by adding age as a predictor variable. The level of statistical significance was set at an α value of .05. Data were handled with SPSS v.12.0 (SPSS Inc, Chicago, Ill).

Results
Among 120 patients recruited to the clinical trial, 102 patients completed cerebral MRI, as well as the self-report of physical and mental health before the operation. We also included one patient who had normal MRI results at follow-up and for whom we assumed normal MRI results at baseline, for a total of 103 patients analyzed (Table 1). Reasons for exclusion of 17 patients from analysis were as follows.

Two patients withdrew from the study for personal reasons. Two patients died in the early postoperative period (one after a stroke and the other suddenly on postoperative day 11). Cerebral MRI results were not obtained at baseline or follow-up from 11 patients, either for pragmatic reasons or because of claustrophobia. The questionnaires from 2 patients were incomplete for summary score calculations. Apart from mean duration of education, the groups included versus excluded from analysis were comparable. We found

### TABLE 1. Baseline and intraoperative characteristics of the patient population

<table>
<thead>
<tr>
<th>Included in analysis (n = 103)</th>
<th>Not included (n = 17)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>64.5 (8.10)</td>
<td>64.2 (7.42)</td>
</tr>
<tr>
<td>Male sex</td>
<td>82 (79.6%)</td>
<td>12 (70.6%)</td>
</tr>
<tr>
<td>Physical health/PCS</td>
<td>41.7 (8.33)</td>
<td>42.5 (6.70)</td>
</tr>
<tr>
<td>Mental health/MCS</td>
<td>42.5 (11.39)</td>
<td>45.3 (12.10)</td>
</tr>
<tr>
<td>Angina class, self-report</td>
<td>No angina</td>
<td>9 (8.7%)</td>
</tr>
<tr>
<td></td>
<td>I</td>
<td>22 (21.4%)</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>37 (35.9%)</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>22 (21.4%)</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>9 (8.7%)</td>
</tr>
<tr>
<td>Missing</td>
<td>4 (3.9%)</td>
<td>1 (5.9%)</td>
</tr>
<tr>
<td>Education, y</td>
<td>10.1 (2.79)</td>
<td>11.7 (3.57)</td>
</tr>
<tr>
<td>Living alone</td>
<td>16 (15.5%)</td>
<td>2 (11.8%)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.7 (3.30)</td>
<td>26.7 (3.81)</td>
</tr>
<tr>
<td>Smoking tobacco daily</td>
<td>18 (17.5%)</td>
<td>4 (23.5%)</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>71.2 (10.19)</td>
<td>71.7 (13.16)</td>
</tr>
<tr>
<td>Previous myocardic infarction</td>
<td>46 (44.7%)</td>
<td>9 (52.9%)</td>
</tr>
<tr>
<td>Previous transitory ischemic attack</td>
<td>4 (3.9%)</td>
<td>1 (5.9%)</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>4 (3.9%)</td>
<td>0</td>
</tr>
<tr>
<td>Serum creatinine, mmol/L</td>
<td>97.4 (16.05)</td>
<td>96.7 (16.47)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>42 (40.8%)</td>
<td>9 (52.9%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>15 (14.6%)</td>
<td>5 (29.4%)</td>
</tr>
<tr>
<td>Obstructive lung disease</td>
<td>12 (11.7%)</td>
<td>3 (17.6%)</td>
</tr>
<tr>
<td>Duration of surgery, min</td>
<td>174.9 (49.99)</td>
<td>189.4 (70.56)</td>
</tr>
<tr>
<td>No. of distal anastomoses</td>
<td>3 (1-5)</td>
<td>3 (1-5)</td>
</tr>
<tr>
<td>Procedures with CPB</td>
<td>56 (54.4%)</td>
<td>11 (64.7%)</td>
</tr>
<tr>
<td>Duration of CPB, min</td>
<td>62.3 (25.12)</td>
<td>73.6 (22.38)</td>
</tr>
<tr>
<td>Cross-over to CPB</td>
<td>4 (3.9%)</td>
<td>3 (17.6%)</td>
</tr>
</tbody>
</table>

Values are presented as counts (percentage), means (standard deviation), or medians (minimum-maximum). PCS, Physical Component Summary of the Short Form 36 Health Survey; MCS, Mental Component Summary of the Short Form 36 Health Survey; CPB, cardiopulmonary bypass. *t Test. †χ² test. ‡Fisher exact test. §Mann-Whitney U test.
a strong linear relationship between age and the existence of cerebral lesions at baseline (Spearman rho = 0.568, P < .000). However, the correlation of age or MRI findings to baseline physical or mental health was not significant (P = .399 for age and physical health, P = .446 for age and mental health; P = .241 for MRI class and physical health, P = .623 for MRI class and mental health).

At 3 months after the operation, preoperative and postoperative health status demonstrated improvement across groups defined by MRI status (Table 2), which is similar to overall effects that have previously been reported.

TABLE 2. Baseline and 3-month physical and mental health summary scores on the basis of cerebral MRI classification

<table>
<thead>
<tr>
<th>Baseline MRI</th>
<th>n</th>
<th>Baseline</th>
<th>3 mo</th>
<th>P value*</th>
<th>Baseline</th>
<th>3 mo</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>19</td>
<td>40.1 (7.34)</td>
<td>47.2 (9.89)</td>
<td>.004</td>
<td>44.1 (9.99)</td>
<td>50.5 (8.47)</td>
<td>.024</td>
</tr>
<tr>
<td>Borderline</td>
<td>38</td>
<td>41.3 (8.67)</td>
<td>44.5 (7.80)</td>
<td>.039</td>
<td>42.1 (11.61)</td>
<td>47.5 (8.55)</td>
<td>.001</td>
</tr>
<tr>
<td>Pathologic</td>
<td>46</td>
<td>42.7 (8.48)</td>
<td>46.7 (8.59)</td>
<td>.002</td>
<td>42.1 (11.90)</td>
<td>48.2 (8.71)</td>
<td>.002</td>
</tr>
</tbody>
</table>

Values are presented as means (standard deviation). MRI, Magnetic resonance imaging. *A paired t test was used for comparison within groups.

In this analysis of covariance model, the amount of variance in total physical health scores explained (adjusted R²) was 38.3%. All predictor variables carried 1 df. Age, education, and life events were discarded from the final model. MRI, Magnetic resonance imaging; CPB, cardiopulmonary bypass. Values of the interaction components were centered to a mean of 0. A model including the same predictor variables, uncentered and without the interaction term, showed significant associations for baseline physical health (F = 19.41, P < .000), relief of angina (F = 12.07, P = .001), and chest wound infection (F = 4.62, P = .034) but not for sex (F = 2.71, P = .103), baseline MRI status (F = 1.18, P = .280), or cardiopulmonary bypass (F = 0.02, P = .904).

Mental Health
Baseline cerebral MRI status (F = 0.637, P = .427), new postoperative cerebral lesions (F = 1.237, P = .269), or an interaction effect of baseline MRI status and use of intraoperative cardiopulmonary bypass (F = 0.188, P = .666) was not predictive of mental health. These 3 models all included the following variables: baseline mental health status, sex, and improved angina.

Discussion
In this study preoperative MRI evidence of cerebral ischemic injury combined with the use of cardiopulmonary bypass was associated with physical health status at 3 months after coronary artery bypass surgery.
For on-pump procedures, no apparent explanation for differences in health status emerged from chart review of intraoperative and postoperative hemodynamics (Table 4). We controlled statistically for conversion from the off-pump to on-pump procedure, postdischarge adverse events, and life stressors. The final model was also stable when adding intraoperative arrhythmia, hypotension, or the use of inotropes.

Measuring physical and mental health status draws on everyday function as experienced by the patient and can be seen as a high level of integration of health domains, including individual coping mechanisms and environmental support. The SF-36 has demonstrated responsiveness in previous studies of cardiac surgery both to improvement and decline. In the present study the physical health component was most sensitive to the interaction phenomenon observed and to relief of angina, whereas our models explained less than 20% of variance in mental health. Newman and coworkers did establish a significant multivariable relationship at 5 years after bypass surgery between cognitive function and physical health but not mental health. A study of aortic arch surgery demonstrated that midterm health status, as measured by the SF-36, was related to the duration of deep hypothermic cardiac arrest. Use of antegrade cerebral perfusion separated groups significantly over varying durations of cardiac arrest with regard to the SF-36 subscales of vitality, physical functioning, and social functioning. Others have found age to be a strong predictor of early and long-term postoperative neurocognitive impairment. In the present study age was strongly correlated with preoperative MRI status. However, the analysis indicated separate contributions of age and preoperative MRI findings on change in physical health, with the strongest contribution coming from MRI status.

**Figure 1. Physical health at 3 months after surgical intervention: change scores from baseline.** Change scores are calculated by subtracting preoperative scores from 3-month total scores. Boxes represent interquartile ranges, and horizontal bands indicate median values. MRI, Magnetic resonance imaging.

**Table 4. Cardiopulmonary bypass group only, intraoperative and postoperative variables**

<table>
<thead>
<tr>
<th>Baseline cerebral MRI</th>
<th>Normal (n = 8)</th>
<th>Borderline/pathologic (n = 48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preinduction SBP, mm Hg</td>
<td>140 (21)</td>
<td>155 (26)</td>
</tr>
<tr>
<td>Minimum intraoperative SBP, mm Hg</td>
<td>73 (8)</td>
<td>74 (10)</td>
</tr>
<tr>
<td>Duration of CPB, min</td>
<td>56 (26)</td>
<td>63 (25)</td>
</tr>
<tr>
<td>Aortic crossclamp time, min</td>
<td>30 (11)</td>
<td>36 (19)</td>
</tr>
<tr>
<td>Maximum MAP during CPB, mm Hg</td>
<td>48 (10)</td>
<td>56 (11)</td>
</tr>
<tr>
<td>Minimum MAP during CPB, mm Hg</td>
<td>36 (4)</td>
<td>37 (8)</td>
</tr>
<tr>
<td>Conversion from off-pump surgery</td>
<td>1 (13%)*</td>
<td>3 (6%)†</td>
</tr>
<tr>
<td>Intraoperative epinephrine</td>
<td>1 (13%)</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>MAP &lt;60 mm Hg occurring in intensive care on day of operation</td>
<td>3 (38%)</td>
<td>11 (23%)</td>
</tr>
<tr>
<td>Postoperative IABP</td>
<td>1 (13%)</td>
<td>0 (—)</td>
</tr>
</tbody>
</table>

Values are presented as means (standard deviation) or counts (percentage). MRI, Magnetic resonance imaging; SBP, systolic blood pressure; CPB, cardiopulmonary bypass; MAP, mean arterial blood pressure; IABP, intra-aortic balloon pump. *Conversion from off-pump procedure for hemodynamic instability. †One conversion for hemodynamic instability and 2 for technical reasons.
It is difficult to explain the mechanisms connecting preoperative evidence of cerebrovascular disease to patient-reported outcomes. We did not find similar results in the group without cardiopulmonary bypass, in which manipulation of the heart during off-pump surgery has the potential to cause episodes of hemodynamic instability and critical cerebral hypoperfusion without hypothermic protection.25 Previous randomized trials of on-pump versus off-pump bypass surgery have failed to demonstrate significant independent effects of cardiopulmonary bypass on patient-reported health status.26-28 In the present study no independent statistical effect was observed of new postoperative lesions on self-reported health. This might indicate that the state of the brain before surgical intervention is of greater importance. A possible explanation is the fact that gaseous and solid microemboli enter the brain during cardiac surgery, with a higher number of emboli during on-pump than off-pump surgery.12,29 Assuming that patients with preoperative cerebral injury have less tolerance for gaseous or solid emboli, diffuse intraoperative cerebral injury would be more extensive among on-pump patients who are exposed to a greater number of emboli. Diffuse cerebral injury after on-pump surgery might disturb the integrity and speed of neural networks, influencing perception, performance, and the experience of rehabilitation without presenting as neurologic symptoms.

As for any secondary analysis, caution must be exercised in the interpretation of results. This study included patients with a low risk profile from a surgical point of view. Although the number of patients with normal preoperative cerebral MRI was relatively low, change in physical health from baseline was well concentrated in the on-pump group at 3 months (Figure 1). Patients without preoperative angina were evenly distributed regarding the use of cardiopulmonary bypass grafting, as well as baseline MRI status. This reduced the possibility of group bias caused by patients experiencing a relative decrease in health status during rehabilitation.20

The amount of missing data at follow-up was low, justifying complete case analysis.

Conclusions
This study strongly suggests that the combination of preoperative cerebral ischemic injury and use of cardiopulmonary bypass can predict postoperative health status at 3 months. Cerebral MRI might be a more specific indicator than age for preoperative assessment of vulnerability or resilience during rehabilitation after on-pump cardiac surgery.

We thank Torbjørn Moum, PhD, for statistical advice and Bjørn Erik Mørk, MSc, and Ellen Hovland for coordinating study patients. The patients generously shared their experiences and made this study possible. Anonymous data for the population reference norms used in this study are from the Health Status Survey 2002 provided by The Norwegian Social Science Data Services (NSD), with data collection and organization conducted by Statistics Norway. Neither Statistics Norway nor NSD are responsible for the analyses or interpretations put forth in this article.

References
20. Pirraglia PA, Peterson JC, Williams-Russo P, Charlson ME. Assessment of decline in health-related quality of life among angina-free


Paper III
Patient-Reported Outcome After Randomization to On-Pump Versus Off-Pump Coronary Artery Surgery

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Departments of Thoracic and Cardiovascular Surgery, and Surgery and The Interventional Center, Rikshospitalet University Hospital, and Oslo University College of Nursing, Oslo, and Institute of Public Health, Faculty of Social Sciences, University of Bergen, Bergen, Norway

Background. Clinical experience with off-pump coronary artery bypass surgery raises the question of a patient experienced benefit compared with on-pump surgery. This prospective and randomized study compared patient-reported outcome between surgical groups, as change scores at 3 months after surgery and longitudinally as time-averaged change from baseline through the first year after surgery.

Methods. In all, 120 patients were randomly assigned to on- or off-pump coronary artery surgery. A questionnaire for patient self-report of angina (Canadian Cardiovascular Society scale), health status (Short Form 36, sleep and sexual difficulty), and overall quality of life (Quality of Life Scale) was administered at baseline and at 3, 6, and 12 months after surgery.

Results. Patient groups were comparable with regard to age, symptoms, comorbidity, and surgical characteristics. Both groups experienced a median of two classes relief of angina at 3 months ($p < 0.0005$), maintained throughout follow-up. Paired $t$ tests revealed significant improvement on all Short Form 36 subscales at 3 months after surgery, with the exception of physical role functioning in the on-pump group. No independent main effects of surgical group were observed in the between-groups covariance models. The longitudinal effect of sex was significant in four Short Form 36 subscales: physical functioning, bodily pain, and role limitation due to physical or emotional problems. Overall quality of life scores were stable in both groups.

Conclusions. Both on-pump and off-pump patients reported less angina and improved health status after surgery. There were no significant differences between surgical groups in health status or overall quality of life, neither cross-sectionally nor longitudinally.

M More than a decade of clinical experience and trials with off-pump coronary artery bypass [1, 2] has resulted in graft patency comparable with on-pump surgery in experienced hands [3–5]. Patient-reported outcomes allow for mapping of the impact of disease and for comparing perceived efficacy and impact of treatment [6]. Heart surgery with cardiopulmonary bypass and temporary cardiac arrest has been associated with neurologic impairment of varying duration and clinical and psychosocial significance [7]. Therefore, it is important to identify a possible impact from procedural redesign to off-pump coronary artery surgery on psychosocial as well as physical domains of patient experience [8]. In the present prospective and randomized study, the aim was to compare patient-reported health related quality of life between surgical groups at 3 months after on- or off-pump coronary artery bypass surgery. Furthermore, a longitudinal comparison was based on postoperative assessments at 3, 6, and 12 months. Health-related quality of life was conceptualized as the subjective assessment of the impact of disease and its treatment across biopsychosocial domains of functioning and well-being [9, 10].

Patients and Methods

Sample

One hundred and twenty patients from southeast Norway were included and randomized in blocks of 20 between March 1999 and March 2002. All patients had stable angina pectoris, were eligible for coronary artery bypass surgery, and had moderate or good left ventricular function. Based on prestudy feasibility analysis, a sex proportion of 22% female was expected. Exclusion criteria were ejection fraction less than 30% or serum creatinine greater than 200 mmol/L, or a lack of ability to read, write, or communicate verbally in Norwegian. Currently, half a standard deviation and 10-point changes on a 0 to 100 health status scale are regarded as clinically significant [11]. Sample size was calculated to detect differences between surgical groups of this magnitude, with 80% power and a two-sided alpha of 0.05.

Procedure

The study protocol was approved by the Regional Ethics Committee (May 23, 1998). After providing written and
informed consent during work-up for coronary artery surgery, the patients completed a researcher administered questionnaire at admission before surgery, and were again seen at outpatient follow-up at 3 and 12 months after surgery. The procedure for all self-assessments was standardized and scheduled before diagnostic procedures or physician interview. At 6 months after surgery, a postal survey was conducted, with a telephone reminder to nonresponders. Randomization to the on- or off-pump procedure was performed after induction of anesthesia. The surgical procedures, and the clinical and neurologic outcomes after 3 months, have previously been reported [12, 13] and only a brief summary follows.

All operations were performed with a balanced opiate, barbiturate, and inhalation anesthesia. The internal mammary artery was used for revascularization of the left anterior descending coronary artery, and saphenous vein grafts for all other vessels. The distal anastomoses were performed first and the proximal anastomoses successively thereafter, using a partial aortic clamp. Graft blood flow was measured with transit time Doppler flow measurement (MediStim, Oslo, Norway) and the graft revised if indicated. At the end of the operation, graft angiography was performed on the table, followed by graft revision if questionable quality of the anastomosis or the graft was revealed. Angiography was performed again after 3 and 12 months in all patients regardless of symptoms.

In the on-pump group, the entire blood-contact surface of the bypass circuit was coated with the Duraflo II heparin surface (Bentley/Baxter, Uden, Netherlands), and activated coagulation time (ACT) was maintained above 480 seconds. All operations were performed under moderate general hypothermia (28°C to 32°C) with topical slushed ice cooling, and cold St. Thomas antegrade cardioplegic solution. Bypass management included membrane oxygenators, arterial line filters, use of a roller pump and cardiotomy suction, nonpulsatile flow of 2.4 L · min⁻¹ · m⁻², and a mean arterial pressure greater than 50 mm Hg.

In the beating heart patients, heparin (1 mg/kg) was administered during take-down of the internal mammary artery, and ACT was maintained above 250 seconds. The distal anastomoses were performed with the use of snares (GoreTex 3-0; W. L. Gore & Associates, Flagstaff, Arizona) and Octopus stabilizers (Medtronics, Minneapolis, Minneapolis), combined with a deep pericardial retraction suture and, as needed, an apical suction device (Starfish; Medtronics). A CO₂ blower (Ethicon Cardiovations, Summerville, New Jersey) was used to obtain a bloodless field.

Questionnaire

Background variables included age, sex, years of education, comorbidity, county of residence, sources of income, whether or not the patient lived alone, depression on the Hospital Anxiety and Depression Scale [14], and illness-related social support [15]. Occurrence of significant life events was reported at follow-up. The following instruments were included at all four time points:

ANGINA. The four-step Canadian Cardiovascular Society scale [16] was translated from English (by L.M., M.A.), slightly modified to facilitate self-report, and anchored to a 4-week time-frame aligning with the Short Form 36.

SHORT FORM 36. The 36-item Medical Outcomes Study Short Form (SF-36) reflects health status during the past 4 weeks on eight subscales: physical functioning, limitations of physical role functioning, bodily pain, general health, vitality, social functioning, limitations of emotional role functioning, and mental health. Raw scores are transformed per manual to a 0 to 100 scale; higher scores indicate better health status [17].

SLEEP. Four items regarding the quality of sleep demonstrated internal consistency (Cronbach’s alpha >0.80) and were summarized as a single index ranging from 4 (lowest quality of sleep) to 23 (uneventful sleep).

Table 1. Baseline and Surgical Characteristics of Patient Population

<table>
<thead>
<tr>
<th>Sex</th>
<th>Off-Pump</th>
<th>On-Pump</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>male:female</td>
<td>52:8</td>
<td>42:18</td>
<td>0.027*</td>
</tr>
<tr>
<td>Age, overall</td>
<td>64.3 ± 7.76</td>
<td>64.7 ± 8.25</td>
<td>0.803b</td>
</tr>
<tr>
<td>Age, male</td>
<td>63.9 ± 7.76</td>
<td>64.5 ± 8.58</td>
<td>0.737b</td>
</tr>
<tr>
<td>Age, female</td>
<td>67.0 ± 7.76</td>
<td>65.2 ± 7.63</td>
<td>0.579b</td>
</tr>
<tr>
<td>Living alone</td>
<td>10</td>
<td>8</td>
<td>0.609*</td>
</tr>
<tr>
<td>Years of education</td>
<td>11 (7–18)</td>
<td>9 (7–18)</td>
<td>0.142c</td>
</tr>
<tr>
<td>Body mass index</td>
<td>26.4 ± 3.49</td>
<td>27.1 ± 3.25</td>
<td>0.247b</td>
</tr>
<tr>
<td>Previous transient ischemic attack or stroke</td>
<td>5</td>
<td>4</td>
<td>1.000d</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>30</td>
<td>25</td>
<td>0.360*</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>71 ± 11.5</td>
<td>72 ± 9.7</td>
<td>0.689g</td>
</tr>
<tr>
<td>Operative time (minutes)</td>
<td>184 (75–385)</td>
<td>155 (90–330)</td>
<td>0.003a</td>
</tr>
<tr>
<td>Distal coronary anastomoses</td>
<td>2.5 (1–5)</td>
<td>3.0 (1–5)</td>
<td>0.202b</td>
</tr>
<tr>
<td>Self-reported comorbidity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>8</td>
<td>9</td>
<td>0.793*</td>
</tr>
<tr>
<td>Hypertension</td>
<td>20</td>
<td>24</td>
<td>0.449a</td>
</tr>
<tr>
<td>Asthma</td>
<td>2</td>
<td>7</td>
<td>0.163d</td>
</tr>
<tr>
<td>Arthritis</td>
<td>5</td>
<td>5</td>
<td>1.000d</td>
</tr>
<tr>
<td>Other chronic diseases</td>
<td>14</td>
<td>24</td>
<td>0.050a</td>
</tr>
<tr>
<td>Total number of comorbidities reported</td>
<td></td>
<td></td>
<td>0.311d</td>
</tr>
<tr>
<td>0</td>
<td>26</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>23</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

a Pearson chi-square. b Student’s t test. c Mann-Whitney test. d Fisher’s exact test.

Values are given as mean ± SD, median (minimum-maximum), or as counts.
SEXUAL DIFFICULTY. A single item was included in the questionnaire to probe for sexual difficulty perceived to be related to the heart disease itself or to its treatment, ranging from 1 (no difficulty experienced) to 7 (greatest difficulty).

OVERALL QUALITY OF LIFE. The 16-item Quality of Life Scale-Norwegian (QOLS-N) yields a single sum score, range 16 to 112, with higher scores indicating better quality of life. The instrument covers relationships and material well-being, health and functioning, and personal, social, and community commitment [18].

Statistical Analysis
Analysis was by intention to treat. Angina pectoris was modeled as a causal indicator influencing health status and overall quality of life [19]. No difference was expected between off-pump and on-pump surgery regarding the effect of surgery on self-reported angina, and significant improvement of health status was expected for both groups. The design was intended to detect clinically significant differences between surgical groups in health status or overall quality of life.

As only 5 patients were lost to follow-up, between-groups tests were based on available cases. Missing items in multi-item scales were replaced with patient-specific mean values for the scale, as long as at least 50% of the scale items were scored by the patient at that assessment. Data management and analysis were handled with SPSS version 12.0 (SPSS, Chicago Illinois). Angina class was treated as ordered categories. For the remaining dependent variables, the cross-sectional comparison of surgical groups used change scores from baseline to 3 months after surgery. Longitudinal comparison was accomplished using time-averaged area under the curve change scores from baseline to 3, 6, and 12 months after surgery, assuming a linear development between assessments. Sex influences the experience of heart disease and cardiac surgery [20], and a two-way analysis of variance model was chosen using baseline scores as covariates. Considering multiple end points and intercorrelations, we set a $p$ value of less than 0.05 as statistically significant for angina and the SF-36 subscales, and $p$ less than 0.01 for sleep, sexual difficulty, and overall quality of life.

Results
Demographic and Background Variables
Baseline data were obtained at median 2 days before surgery. The two groups were similar regarding demographic variables at baseline except for sex (Table 1). Sex was significantly related to number of comorbidities, ejection fraction, education, sleep index, and to all SF-36 subscales except mental health, but not to sexual difficulty or overall quality of life (data not shown). However, no statistical difference was found between surgical groups overall (Fig 1) or by sex regarding angina class at baseline (between-groups Fisher’s exact test: female $p = 0.452$, male $p = 0.132$).

All 120 randomized patients underwent surgery. Seven patients were converted from off-pump to on-pump surgery: 2 for hemodynamic instability and 5 after intraoperative angiography. There were 2 in-hospital deaths, 1 female in each surgical group. Of 3 patients withdrawn from follow-up in the off-pump group, 1 provided no reason for withdrawal, 1 rescheduled repeatedly but failed to appear for any of the follow-up appointments, and 1 patient completed the 3-month assessment before...
withdrawal due to progression of other and noncardiac disease. Comparison at baseline excluding the 5 noncompleters did not alter the balance between groups. At 12 months after surgery, neither change of marital status or source of income, nor the number of significant life events experienced during the previous year differed significantly between the groups. The angiographic patency did not differ between the groups at 3 and 12 months [13].

**Angina**

Angina was significantly relieved in both surgical groups at 3 months after bypass surgery (Wilcoxon signed ranks, within-groups analysis, \( p < 0.0005 \)) with a median improvement of 2 angina scale steps. There were no significant differences in distribution of scores between surgical groups at 3 months (Fig 1), 6 months (Fisher’s exact test, \( p = 0.617 \)), or 12 months (\( p = 0.809 \)), supporting our first hypothesis. Broken down by preoperative angina class, change scores confirmed an equal distribution of results between groups.

**Health Status**

Baseline and change scores of health status and overall quality of life are detailed in Tables 2 and 3. Both groups improved significantly on all SF-36 subscales from baseline to 3 months after surgery (paired \( t \) tests of total scores, data not shown), with the exception of limitations in physical role functioning in the on-pump group. Controlling for baseline scores, there was a main effect of procedure in the social functioning domain at 3 months. However, this effect was not independent but appeared in interaction with sex. The interaction effect size was small, and the covariance model explained 36.5% of domain variance.

Sexual difficulty was significantly reduced in the off-pump group at 3 months (paired \( t \) test, \( p = 0.001 \)), and in both groups at 12 months (\( p < 0.01 \)). At 3 months, the quality of sleep changed in opposite though nonsignificant trends within groups. Controlling for sex and baseline data, no significant differences were found between surgical groups regarding sleep or sexual difficulty.

Comparison of time-averaged change scores at 12 months revealed no significant differences between surgical groups. Among the SF-36 subscales, sex was identified as a significant independent variable in four of eight domains: physical functioning, bodily pain, role limitation due to physical or emotional problems. All effect sizes were small with \( \eta^2 \) less than 0.1. No interaction effect was detected between sex and procedure.

**Overall Quality of Life**

No significant differences between surgical groups were demonstrated in the cross-sectional or longitudinal covariance model. The stability of overall quality of life was

### Table 2. Baseline Scores and Change Scores at 3 Months by Surgical Group

<table>
<thead>
<tr>
<th>Domain</th>
<th>Off-Pump</th>
<th>On-Pump</th>
<th>n</th>
<th>( p ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PF</td>
<td>58.8 (23.05)</td>
<td>57.8 (20.88)</td>
<td>60/60</td>
<td>0.687</td>
</tr>
<tr>
<td>RP</td>
<td>23.3 (34.71)</td>
<td>21.4 (36.39)</td>
<td>60/59</td>
<td>0.893</td>
</tr>
<tr>
<td>BP</td>
<td>53.2 (20.12)</td>
<td>53.0 (21.72)</td>
<td>60/60</td>
<td>0.898</td>
</tr>
<tr>
<td>GH</td>
<td>61.5 (19.17)</td>
<td>54.0 (21.24)</td>
<td>60/60</td>
<td>0.064</td>
</tr>
<tr>
<td>VT</td>
<td>48.5 (19.07)</td>
<td>42.9 (19.67)</td>
<td>60/60</td>
<td>0.129</td>
</tr>
<tr>
<td>SF</td>
<td>71.9 (23.65)</td>
<td>69.8 (21.87)</td>
<td>60/60</td>
<td>0.640</td>
</tr>
<tr>
<td>RE</td>
<td>48.6 (44.34)</td>
<td>45.2 (43.66)</td>
<td>59/59</td>
<td>0.458</td>
</tr>
<tr>
<td>MH</td>
<td>73.1 (19.12)</td>
<td>69.6 (15.85)</td>
<td>60/60</td>
<td>0.202</td>
</tr>
<tr>
<td>Sleep</td>
<td>17.4 (4.19)</td>
<td>18.0 (3.70)</td>
<td>60/59</td>
<td>0.463</td>
</tr>
<tr>
<td>Sexual difficulty</td>
<td>3.6 (1.95)</td>
<td>3.0 (2.03)</td>
<td>58/59</td>
<td>0.490</td>
</tr>
<tr>
<td>QOLS-N</td>
<td>87.6 (10.45)</td>
<td>85.7 (9.85)</td>
<td>60/60</td>
<td>0.264</td>
</tr>
</tbody>
</table>

* \( p = 0.029 \) (F 4.9) for surgical group, \( p = 0.008 \) (F 7.2) for interaction effect of sex and procedure, \( p = 0.025 \) (F 5.1) for effect of sex.

Values are given as mean (SD). Baseline group comparison was performed with an analysis of variance model, using surgical group and sex as independent variables. Three-month change scores are unadjusted means for surgical group. Analysis of covariance models were estimated using group and gender as independent variables, and the baseline value of each domain as a covariate.

BP = bodily pain; GH = general health; MH = mental health; PF = physical function; QOLS-N = Quality of Life Scale/Norwegian; RE = role limitation caused by emotional problems; RP = role limitation caused by physical problems; SF = social function; VT = vitality.

### Table 3. Time-Averaged Change Scores at 12 Months

<table>
<thead>
<tr>
<th>Domain</th>
<th>Off-Pump</th>
<th>On-Pump</th>
<th>n</th>
<th>( p ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PF</td>
<td>18.4 (20.53)</td>
<td>14.1 (20.94)</td>
<td>57/59</td>
<td>0.257</td>
</tr>
<tr>
<td>RP</td>
<td>12.7 (46.80)</td>
<td>7.8 (40.07)</td>
<td>57/58</td>
<td>0.735</td>
</tr>
<tr>
<td>BP</td>
<td>14.4 (25.45)</td>
<td>6.6 (22.06)</td>
<td>57/59</td>
<td>0.162</td>
</tr>
<tr>
<td>GH</td>
<td>7.8 (17.50)</td>
<td>14.6 (20.19)</td>
<td>57/59</td>
<td>0.137</td>
</tr>
<tr>
<td>VT</td>
<td>9.4 (19.20)</td>
<td>12.0 (20.78)</td>
<td>57/59</td>
<td>0.961</td>
</tr>
<tr>
<td>SF</td>
<td>8.1 (25.61)</td>
<td>10.4 (24.25)</td>
<td>57/59</td>
<td>0.029a</td>
</tr>
<tr>
<td>RE</td>
<td>26.8 (44.82)</td>
<td>25.9 (52.26)</td>
<td>56/58</td>
<td>0.456</td>
</tr>
<tr>
<td>MH</td>
<td>8.8 (14.76)</td>
<td>8.2 (15.19)</td>
<td>57/59</td>
<td>0.241</td>
</tr>
<tr>
<td>Sleep</td>
<td>0.7 (3.63)</td>
<td>-0.4 (3.91)</td>
<td>57/59</td>
<td>0.606</td>
</tr>
<tr>
<td>Sexual difficulty</td>
<td>-0.9 (2.05)</td>
<td>-0.5 (1.88)</td>
<td>54/58</td>
<td>0.907</td>
</tr>
<tr>
<td>QOLS-N</td>
<td>1.6 (8.79)</td>
<td>0.9 (10.53)</td>
<td>57/59</td>
<td>0.741</td>
</tr>
</tbody>
</table>

Values are given as mean (SD). Baseline group comparison was performed with an analysis of variance model, using surgical group and sex as independent variables. Three-month change scores are unadjusted means for surgical group. Analysis of covariance models were estimated using group and gender as independent variables, and the baseline value of each domain as a covariate.

BP = bodily pain; GH = general health; MH = mental health; PF = physical function; QOLS-N = Quality of Life Scale/Norwegian; RE = role limitation caused by emotional problems; RP = role limitation caused by physical problems; SF = social function; VT = vitality.

* Log-transformation of scores were used in the between-groups analysis.
evident in total scores on the Quality of Life Scale at all three follow-up assessments, with an exception from baseline to 12 months for the off-pump group as a whole (paired t tests, mean improvement 3.0 points [SD 8.29], p = 0.010).

Comment

We used a simple angina classification for self-report by patients, evaluated separately from clinical assessments and testing. A few patients did acknowledge uncertainty in differentiating nonanginal chest discomfort from angina at follow-up. As residual nonanginal chest pain may be prevalent after bypass surgery [21], patient counseling remains important to assist interpretation of chest discomfort. At 1 year after surgery, 26.8% of patients (15 of 56) in the off-pump group and 24.1% (14 of 58) in the on-pump group reported some degree of angina. By that time, 9 patients had undergone percutaneous coronary artery procedures, 5 in the off-pump group (6 procedures) and 3 in the on-pump group where an additional patient had coronary intervention pending. Assuming comparable self-report methodology, these percentages are similar to a cohort study of 577 patients with advanced coronary artery disease where 27% reported chest pain at 1 year after bypass surgery [22]. In contrast, the Bristol group pooled follow-up of 401 patients at 1 and 2 years reported 14% with recurrent angina in the on-pump group compared with 12% in the off-pump group [3]. For available cases, we determined improvement of angina versus no change or worsening at follow-up. We then analyzed the influence of surgical group and sex on improvement in a logistic regression model, finding no significant influence at 3 months (n = 107), or 12 months (n = 110), 6 months (n = 107), or 12 months (n = 109). As reported earlier from this sample, postoperative characteristics were statistically comparable between surgical groups, except for greater mean postoperative bleeding in the off-pump group. In the on-pump group, the number of major complications did not statistically separate the surgical groups but did include 1 case of mediastinitis and 2 incidents of stroke, 1 fatal and 1 patient recovering completely [13].

The SF-36 has demonstrated postoperative responsiveness in previous studies of heart surgery, both to improvement [23] and decline [24], with preoperative scores as a major determinant of predicted change [25]. The social functioning subscale reflects interference with social activities from physical or emotional problems. In this domain, we found a significant interaction effect of surgical procedure and sex, limited to the comparison at 3 months and not mirrored in other psychosocial domains including sleep and sexual difficulties. The overall mean female score at baseline was 11.7 points lower than the by sex and age group comparable normal Norwegian population [26], implying a potential for improvement. At 3 months, the female scores heterogeneously diverged by surgical group while male scores improved in both groups. We were unable to explain this finding by loss of graft patency, or by adding social support, depression, marital status, and life events to a regression model. The initial finding was augmented by a trend among male respondents toward limitation by maximum possible subscale score (ceiling effect), increasing the pull of lower scores. Furthermore, the smaller female off-pump subgroup included 1 person to be withdrawn for noncardiac disease. Repeat analysis excluding this individual removed the statistical significance of procedure without changing results on other outcomes.

Among the previously published randomized and prospective studies including patient-reported outcomes, one reported angina but not health status [3]. However, data were obtained from 328 of 401 randomized patients in this cohort at median 3 years’ follow-up in a posttest only design, finding no significant differences between surgical groups regarding disease specific or general health status [27]. A Dutch multicenter study prospectively included health status outcome but not self-reported angina, finding no significant differences between the on-pump and off-pump group at 3 and 12 months after surgery [28]. A single-center trial reported similar cardiac and patient-reported outcomes at 1 year after surgery [5]. Summing up, there is currently no evidence from randomized trials to support a claim of different self-reported health status at 3 months or 1 year after surgery. It does not appear that the possible benefit of avoiding cardiopulmonary bypass is of sufficient size in itself, or relative to the risk inherent in the more challenging off-pump procedure, to show up in a broad range of patient-reported outcomes including physical as well as psychosocial domains. Our findings align with the objective, neuropsychological tests earlier reported [28], although one would not have been surprised to observe self-report reflecting psychosocial aspects that cognitive tests might not reveal. As in the other randomized studies, this study was not powered to detect small effect sizes of possible clinical significance and in the range of 2 to 5 points, which are relevant in epidemiologic studies but require too large a number for the smaller randomized trials. Also, the variance in health status scores may not only reflect interindividual variation, but suggests consideration of the whole mosaic of surgical treatment, where use of cardiopulmonary bypass is but one element of the pathway from admission to completed outpatient rehabilitation.

Some limitations of our study should be acknowledged. First, while both procedures were effective more than 12 months without statistically significant differences, this study of low-risk patients was not designed to prove equivalence or map outcomes beyond the first year after surgery. Sex stratification could have improved our study design. We studied development beyond the early postoperative recovery period, obscuring possible short-term group differences after hospital discharge. However, our questionnaire requested patients’ perceptions during the last 4 weeks, suggesting that the experience of postoperative week 8 to 12 would be represented in our material. While blinding until induction of anesthesia was accomplished, the medical chart could not be blinded after surgery, limiting full control over untoward disclosure of procedure. Available knowledge at the start of inclusion suggested a
broad design with multiple indicators, as surgical innovations may have unknown and unforeseen effects that are latent in nonrandomized designs but do show up in a randomized trial. Thus, additional risk of type I error was accepted. Although the overall amount of missing data were considered minimal, a possibility of informative censoring could not be excluded. We repeated the analysis with an augmented data set, constructed according to the assumed nature of missingness. All results concurred with those of the initial analysis.

Our sample was smaller than the multicenter study reported by van Dijk and coworkers [28]. However, a prospective single-center trial offers greater control of standardization and reduces interviewer and institution bias. We were able to enroll all patients approached, and to randomize all patients recruited, thus reducing selection bias within our low-risk patient group. By deferring randomization until after induction of anesthesia, no instances of cross-over from the on-pump to the off-pump group occurred, which is unique compared with the other clinical trials prospectively reporting on health status outcomes [5, 28].

In conclusion, this randomized trial of patient-reported outcomes after on-pump versus off-pump coronary artery bypass surgery was powered to detect moderate size effect differences. Questioning patients on symptoms, health status, and overall quality of life at 3, 6, and 12 months after surgery revealed significant improvement in symptoms and health status within both surgical groups. There were no significant differences in health status or overall quality of life between groups, cross-sectionally or longitudinally, explained by independent main effects of surgical procedure.

The assistance of biostatistician Geir Aamodt, PhD, is gratefully acknowledged. Financial support for this study was provided by the Research Council of Norway (NFR2004–160347), Norwegian Nurses' Association, Norwegian Association of Heart and Lung Patients, and Center for Nursing Research and Patient Participation at Rikshospitalet University Hospital.

References

Paper IV
Quality of life can both influence and be an outcome of general health perceptions after heart surgery

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* Corresponding author

Abstract

Background: Our aim was to investigate the existence of a reciprocal relationship between patients’ assessment of quality of life and their appraisal of health. If present, this relationship will interfere with the interpretation of heart surgery’s effect on overall quality of life.

Methods: Path analysis was used to investigate reciprocal causal relationships between general health perceptions and overall quality of life before and after heart surgery. Longitudinal data from a study of coronary artery bypass surgery were used to model lagged, cross-lagged, and simultaneous paths over four time-points of assessment from before surgery to one year afterwards. The conceptual framework for the analysis was the Wilson and Cleary causal pathway model. General health perceptions were measured with the Short Form 36. Overall quality of life was measured with i) a single question regarding life satisfaction and ii) the multi-item Quality of Life Survey.

Results: Acceptable model fit was obtained for reciprocal causation between general health perceptions and overall quality of life. Regression coefficients changed over different phases of rehabilitation. Serial correlation accounted for much of the variance within variables over time.

Conclusion: The present analysis demonstrates that unidirectional models of causality are inadequate to explain the effect of heart surgery on overall quality of life. Overall quality of life can causally influence as well as be an outcome of health status after coronary artery bypass surgery.

Background

Practice guidelines for chronic stable angina and for the coronary artery bypass operation target improvement of survival and symptomatic relief of angina [1], with improvement of the quality of life (QoL) as an expected secondary outcome [2]. Although a consensus exists on the subjective nature of QoL, the issues of what to measure and how to interpret the results remain areas of con-
troversy [3]. Meanwhile, the number of papers returned from a database query of 'QoL and coronary artery bypass surgery' average one per week for every year of the last five years, and clinicians face the task of judging the validity and significance of this research [4]. The interpretation of results from correlation research may generate assumptions of causality. If disease is a predictor of health, and health has an effect on QoL, then therapies reducing the burden of disease are expected to improve QoL. On the other hand, if the patient's appraisal of QoL is not only an outcome, but also affects the perception of health, then the expectation that surgery can improve QoL may be too simplistic. In other words, reciprocal causality will interfere with the interpretation of heart surgery's effect on overall quality of life. Valid and reliable measures of QoL remain at risk of being labeled 'unresponsive' unless this latent controversy is understood and resolved. In clinical practice, evidence of reciprocal causality can support pre-operative screening for patients who rate their QoL as poor, to guide complementary interventions during rehabilitation to ensure that outcomes following surgery are maximized. In this study, our aim was to investigate the existence of a reciprocal relationship between patients' assessment of quality of life and their appraisal of health.

Theoretical framework

In 1995, Wilson and Cleary proposed a causal pathway model to link clinical variables to QoL (Figure 1), in order to connect the field of objective measurement to that of subjective experience [5].

This model has influenced the analysis of data from cardiac [6-8] and other patient populations [9,10]. Wilson and Cleary structured outcomes along a continuum of increasing complexity from biological parameters through symptom status, functional status, general health perceptions and overall QoL [5]. General health perceptions reflect the functional status and symptoms such as angina pectoris [5], and are important for their predictive ability on the use of health care services as well as mortality [11]. Wilson and Cleary used the concepts health status and health-related QoL interchangeably in the description of their model. However, both concepts appear clearly separate from overall QoL, which represents "a stable synthesis of a wide range of experiences and feelings that people have" [5]. Interaction effects of individual and environmental characteristics may occur at each level of outcomes.

Previous research citing Wilson and Cleary has modeled unidirectional causal effects from general health perceptions towards overall QoL [6-10], under the assumption that the dominant path of causality is sufficient to guide data analysis. However, interpretation of results is conditional upon the absence of significant reciprocal effects. It is debatable whether QoL represents a summary outcome of different and situational life aspects, or a "top-down" individual disposition towards the evaluation of life aspects [12,13]. Integration of these theoretical positions in a reciprocal causality model of "top-down" personality factors and "bottom-up" situational variables has been proposed [14,15]. With repeated measurements of health status and overall QoL in patients undergoing heart surgery, an opportunity exists to challenge the conventional direction of causality illustrated in Figure 1, and assess the strength of causal relationships over time. If reciprocal causality is possible and the mechanisms can be explained, the Wilson and Cleary model must be accepted as more complex than previously recognized in correlation research.

Methods

Patient sample

The data set came from a previously reported [16] randomized clinical study of on-pump versus off-pump coronary artery bypass surgery. The parent study recruited and included 120 patients between 40 and 80 years of age, with stable angina pectoris and moderate or good left ventricular function. Exclusion criteria were ejection fraction < 30 % and/or renal failure (serum creatinine > 200 mmol/L), as well as patients unable to read, write or communicate verbally in Norwegian. The study protocol was approved by the Regional Ethics Committee, and patients provided written and informed consent. Five patients were lost to follow-up due to mortality (2 patients) and withdrawal (3 patients).

Figure 1

For the present path analysis, the patients constituted one group, as no significant effect of randomization to either treatment arm was found [16]. Complete sets of data were required for the analysis, resulting in the exclusion from analysis of seven more patients where one or more data points were missing. Thus, the patient sample for the present study included 108 complete sets out of 120 potential sets of patient data, representing individuals (81 % men) between 47 and 79 years (mean age 64.2 years). The patients were comparable to the parent study population on all subscales of the SF-36 health status survey. These individuals reported a median angina score of Canadian Cardiovascular Society class II [17], and 44 % had previously experienced myocardial infarction.

Procedure
A study database provided demographic data and clinical parameters. The patients completed a questionnaire 4 times; at hospital admission before surgery (baseline), and 3, 6 (questionnaire sent by mail) and 12 months after surgery (follow-up visits at months 3 and 12). While the questionnaire also included outcome measures such as symptoms and functional status, the data analyzed in the present paper only concern overall quality of life and general health perceptions. All in-patient assessments were scheduled before any further clinical or research diagnostics.

Self-reported variables
Overall quality of life
Overall QoL can be measured in different ways depending on the substantive focus of investigation, such as happiness, well-being, life satisfaction [18]. The theoretical rationale and explicit ambition of the Wilson and Cleary model, integration of the biomedical and social sciences, suggested the use of life satisfaction instruments to represent overall quality of life [5]. Two instruments, Global Quality of Life (gQoL) and a Norwegian version of the Quality of Life Survey (QoLS-N), were used in order to assess the influence of methods' effects.

Global Quality of Life, previously used in epidemiological research [19], is a single-item overall appraisal of satisfaction with current life, scored on a seven step Likert-type scale: "Thinking about your life at the moment, would you say that you by and large are satisfied with life, or are you mostly dissatisfied?". The labeled response options ranged from 'very dissatisfied' to 'very satisfied' from the validated translation [18]. Internal consistency (Cronbach's alpha) of the QoLS-N is reported at 0.86, with a test-retest reliability of 0.83 [21]. In this study, internal consistency was 0.83 at baseline and 0.90 at all subsequent time-points.

General health perceptions
We used the General Health subscale from the Short Form 36 (SF-36 version 1.2) as a single indicator. The 5 general health items cover current health, health outlook, and resistance to illness. Scores range from 0–100 points; higher scores indicate better health. Internal consistency (Cronbach's alpha) for this subscale has been reported at 0.84 [22] and varied in our study from 0.73 at baseline and three months' assessment, to 0.78 (six months) and 0.81 (twelve months). General health perceptions are associated with physical, mental and social health domains [23].

Statistical analysis
We modeled causal paths with longitudinal data between single indicator variables for overall quality of life and general health perceptions. The path analysis used structural equation modeling [24] where all 4 time-points were represented in all models tested. This method allows the inclusion of feedback or reciprocal paths in addition to unidirectional causal effects [25] and is therefore more appropriate for our study than standard multiple regression technique. Figure 2 illustrates the two different sets of reciprocal relationships that were modeled. Cross-lagged components model the causal effect as observed at a later point in time (Figure 2a), while simultaneous components are observed at the same time (Figure 2b).

Structural equation modeling does not prove causality, but it tests whether the data set, with its inherent covariance structure, supports or rejects the postulated effects. Thus, the data matrix under analysis is the set of covariances between all pairs of variables. The interrelationships of the observed variables are specified in structural equations by the researcher, according to hypotheses and theories. Adding, removing or changing the direction of an effect (arrow in Figure 2) means changing the set of regression equations. The combination of all equations form a model, and the fit or appropriateness of this model is tested by analyzing all equations simultaneously, looking at the whole landscape rather than the individual parts. The result of analysis is expressed as a set of fit indices, indicating how well the specified model fits the observed reality. The task of interpretation is to accept, reject, or possibly modify the paths included in the model.

Scoring of the SF-36 was completed according to the manual [23] using the SPSS version 12.0 (SPSS Inc., Chicago IL). To analyze the extent of selective attrition, \( \chi^2 \) and t-
tests for independent samples were used. Histograms and
descriptive statistics for the individual variables were
screened for deviations from normality. The distribution
of scores indicated reasonable compliance with the
assumptions of linear modeling. The covariance matrix
was analyzed using maximum likelihood estimation in
Lisrel version 8.72 (Scientific Software International, Lin-
colnwood IL). We allowed for each effect component to
vary over time. First, we modeled the time-lagged effects
between general health perceptions and overall QoL over
4 time-points. We included correlations between variables
measured at the same occasion to take into account the
presence of confounding variables [25,26]. The second
model included the cross-lagged effects between the dif-
ferent variables to the following time-point of assessment.
Finally, a third model was introduced to evaluate simulta-
neous effects, where the correlation between variables
voiced at time X were replaced by reciprocal causal effects. A series of model
fit characteristics were used to evaluate the adequacy of
was analyzed using maximum likelihood estimation in
Lisrel version 8.72 (Scientific Software International, Lin-
colnwood IL). We allowed for each effect component to
vary over time. First, we modeled the time-lagged effects
between general health perceptions and overall QoL over
4 time-points. We included correlations between variables
measured at the same occasion to take into account the
presence of confounding variables [25,26]. The second
model included the cross-lagged effects between the dif-
ferent variables to the following time-point of assessment.
Finally, a third model was introduced to evaluate simulta-
neous effects, where the correlation between variables
voiced at time X were replaced by reciprocal causal effects. A series of model

Figure 2
Reciprocal causal paths, illustrating a) cross-lagged
effects and b) simultaneous effects. Single arrows indi-
cate causal paths. Only two time-points are illustrated, while
four time-points were analyzed in all models reported in this
paper.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{fig2.png}
\caption{Reciprocal causal paths, illustrating a) cross-lagged
effects and b) simultaneous effects. Single arrows indi-
cate causal paths. Only two time-points are illustrated, while
four time-points were analyzed in all models reported in this
paper.}
\end{figure}

\textbf{Results}

General health and QoL measurements at all time-points
were evaluated with a \( \chi^2 \) difference test using a critical value (alpha) of 5 \%.

\textbf{Structural equation modeling of global Quality of Life
(gQoL)}

Full versions of the cross-lagged and simultaneous path
models, with unstandardized estimates of the paths as
well as correlations of the error variances of the variables,
are available under Additional files. The abbreviated ver-
sions in Figure 3 and 4 serve to outline the main results
with standardized regression coefficients.

At all assessments, the individual patient scores on the
global Quality of Life item (gQoL) covered the full scale
range from 1 to 7. The group mean gQoL improved from
5.0 before surgery to 5.6 at 12 months' follow-up (Table
1). Overall QoL scores measured with the QoLS-N also
demonstrated individual variation; the group mean at
baseline was 86.5 points increasing to 88.1 after 12
months, while individual scores ranged from 52.6 to 112
points during the same time-span.
lagged effect from overall QoL at baseline to the three months assessment of general health was present, indicating independent predictor properties of the baseline QoL appraisal during the greatest change in general health status. This model fitted the data well (Table 3) although the change in $\chi^2$ compared to the lagged model was not statistically significant. The simultaneous reciprocal model (Figure 4) demonstrated best fit and, by chi-square test, a significant model improvement, with significant path coefficients observed at three and six months after surgery from overall QoL toward general health perceptions (see also Additional file 2: Additional file 2_simultaneous_gQOL.pdf). To contrast this analysis with an assumption of no causal effects, we set the bidirectional paths within each time-point to equal size. This resulted in an unidentifiable model.

### Structural equation modeling of the Quality of Life Survey (QoLS-N)

We re-ran the previous analyses with the QoLS-N results (Table 3). Full versions of the cross-lagged and simultaneous path models are available as Additional files 3 and 4 (Additional file 3_xlagged_QOLS.pdf, and Additional file 4_simultaneous_QOLS.pdf). By fitting identical models with the two instruments, it was possible to assess the extent of instrument-specific results, which constitutes a step towards cross-validation (Figure 5).

In the cross-lagged model, the path from general health at six months to QoL at 12 months was statistically significant. Each point increase in general health at six months, resulting from all directional paths assigned, was associated with 0.11 point increase in QoLS-N at one year after surgery.
surgery. In the simultaneous reciprocal model, significant standardized regression coefficients from QoL to general health dominated at 3 and 6 months after surgery (0.26 and 0.28, respectively), while the reverse effect from general health towards QoL (0.27) was present at one year after surgery. However, the model fit indices suggested that the cross-lagged model was superior to the model allowing simultaneous and bidirectional causal paths (Table 3). Cross-lagged effects also demonstrated better model fit than two unidirectional and simultaneous effects models, either according to the conventional paths of the Wilson and Cleary model or with reversed causation only – from QoL towards general health. An extended version of Table 3 details the latter results and is available on request.

**Discussion**

In this study, structural equation modeling supported the existence of reciprocal causal paths between general health perceptions and overall QoL. Our longitudinal analysis indicated that changes in general health perceptions may be conditional upon as well as contributing to the appraisal of overall QoL. The clinical implication is that the evidence used for preoperative counseling on expected changes in symptoms and functioning, should not be extrapolated to general health or life satisfaction following coronary artery bypass surgery. Restraining the level of abstraction to outcomes that are conceptually closer to clinical parameters and the surgical intervention, such as symptoms and functional status domains [5], may prevent misunderstandings and facilitate joint decision-making between patient and provider. Bearing on research, the present study describes a potential source of error when interpreting cross-sectional associations between overall QoL, general health, and heart surgery.

We based our analysis on research demonstrating that general health perceptions and overall QoL represent conceptually and empirically distinct dimensions [27]. Previous studies of heart patients where the Wilson and Cleary model has been evaluated as a conceptual framework, present different interpretations of overall QoL: either as life satisfaction similar to the present study [6], or by referring to health-related QoL (HQoL) [28], or disease-specific health-related QoL [7]. If the main causal direction from general health perceptions towards overall QoL were dominant, blurring of the conceptual distinction between health status or HQoL and overall QoL would be less consequential, although possibly not desirable [3]. However, our results indicate a more complex causal network, which precludes conceptualizing overall QoL as health or subsumed within health. Examples from neighbor research fields expand on the causal networks involved, where explanatory variables associated with overall QoL include a genetic component [29,30], personality trait characteristics [31], and – in cardiac patients – life orientation or Sense of Coherence [32].

In our study, the regression coefficients between general health perceptions and overall QoL did not demonstrate a stable pattern. This variation may represent true variation of structurally stable constructs, or there may be unidentified structural variation due to response shifts from changing values or beliefs of respondents [33], possibly mediated by alterations in cognitive processing after heart surgery. Sample size was in this study insufficient for

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**Table 3: Model fit indices**

<table>
<thead>
<tr>
<th></th>
<th>χ²</th>
<th>df</th>
<th>p</th>
<th>RMSEA</th>
<th>CFI</th>
<th>SRMR</th>
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<th>∆df</th>
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<td>1. Lagged effects only</td>
<td>18.55</td>
<td>12</td>
<td>.100</td>
<td>.072 a</td>
<td>.990</td>
<td>.125</td>
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<td>2. Cross-lagged effects</td>
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<td>.132</td>
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<td>.990</td>
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<td>7.21</td>
<td>6</td>
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<td>6. Simultaneous effects</td>
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<td>9</td>
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<td>.01</td>
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a p of Close Fit >.05, the null hypothesis is RMSEA <.05.
b P < .05
c The 90% confidence interval is .018 to .161

CFI Comparative Fit Index, values > 0.90 indicates a good fit of the model.
RMSEA Root Mean Square Error of Approximation, values < 0.08 indicating acceptable, and < 0.05 good fit of the residuals.
SRMR Standardized Root Mean Residual, values < 0.10 indicating good fit.
∆χ² Difference in degrees of freedom from reference model
∆df Difference in chi-square from reference model chi square
Surgery may alter the relative strength of bidirectional feedback, whereas positive health transitions following severe health impairments may trigger through negative feedback. The set point occurs from contributing domains [13]. Homeostasis are triggered when a challenge to an individual occurs from contributing domains [13]. The adequacy of the lagged effects across patient groups. The adequacy of the lagged effects modeling of latent variables to control for time invariance of item factor loadings on each construct. However, we used instruments where the variance was fully modeled – as in the case of the single-item gQoL – or where the factor structure and reliability has been extensively reported across patient groups. The adequacy of the lagged effects models suggested that longitudinal construct validity was satisfactory. A homeostatic concept of subjective well-being offers a possible explanation to the changing "bottom-up" and "top-down" causal paths over situations and time. It has been suggested that mechanisms to restore homeostasis are triggered when a challenge to an individual set point occurs from contributing domains [13]. Severe health impairments may trigger through negative feedback, whereas positive health transitions following surgery may alter the relative strength of bidirectional paths connecting health perceptions and QoL. In the present study, the patients were in a transition from a preoperative state through rehabilitation. During the period of greatest change in general health perceptions, from preoperative status to three months after surgery, paths from overall QoL towards general health appeared dominant in the simultaneous effects models (gQoL and QoLS-N) as well as in the cross-lagged model using gQoL observations. In contrast, the cross-lagged QoLS-N model was indifferent from baseline to three months after surgery. Furthermore, from six months to one year after surgery and during less magnitude of health transition, the regression coefficients in the conventional direction from general health perceptions towards overall QoL were significant in the cross-lagged and simultaneous effects QoLS-N models (Figure 5, Additional file 3: Additional
file 3_xlagged_QOLS-N, and Additional file 4: Additional file 4_simultaneous_QOLS-N).

Variation between regression coefficients were in the present study associated with the choice of overall QoL instrument. While a consensus exists as to how QoL should be assessed, i.e. as a subjective appraisal obtained by asking the patient [34], there is no gold standard or reference criterion for evaluation of content validity of overall QoL instruments [35]. In our observations, we selected measures that emphasize life satisfaction as a critical component of overall QoL. It should be noted that Wilson and Cleary [5] also cite subjective well-being and happiness along with life satisfaction as representative for overall QoL, although their paper does not enter the discussion on structural relationships of indicators of overall QoL. The correlation matrix of Table 2 indicates only a moderate overlap of content between the gQoL and the QoLS-N. Their intercorrelation coefficients remain below 0.60, and the extent of common methods variance is unknown. Two complementary explanations may be offered for the modest strength of association and the different results obtained when modeling with different instruments: First, compared to the QoLS-N, the single-item gQoL emphasizes “top-down” effects towards general health perceptions during changing health conditions. It is possible that the single question favors a life orientation response, as the response options neither are anchored to specific life domains nor impose any assumptions of weighting due to the number or order of items. Conversely, the sum score of the QoLS-N may represent a bottom-up perspective of overall QoL as a sum of experiences and appraisals. However, although the selection of items is empirically grounded [20], each item is given equal weight in the summary score and this may not adequately reflect the preferences and priorities held by respondents.

Second, one may question whether the gQoL and the QOLS-N represent the same latent variable, life satisfaction. Exploring their relationships, we correlated the gQoL at baseline and at one year after surgery with a three-factor solution of the QOLS derived from analysis of healthy subjects’ responses [20]. Amongst these factors, Health and Functioning demonstrated the greatest strength of association to the gQoL, followed by Relationships and Material Well-Being and finally Personal, Social and Community Commitment. Of note, the QoLS-N scale contains one item specifying physical health. To control for uncontrolled loss of variance and inflated regression coefficients between the observed variables in our analyses, we ran separate models with a 15-item modification of the QoLS-N score in which the health item was deleted. No substantial change in model fit was observed (data available on request).

Some limitations of this study should be acknowledged. We assumed that the baseline values of our observed variables carried adequate adjustment for numerous candidate background variables such as gender, age, socioeconomic status, level of education and co-morbidity. A larger sample size would allow for more parameters and variables – observed or latent – to be included. However, our analysis used the p of Close Fit indicator (see legend, Table 3) to provide an estimate of sufficient power to detect poor model fit due to misspecification. As this study is an early investigation of reciprocal effects, we could not locate publications that could validate the tim-

![Diagram of significant a) cross-lagged and b) simultaneous paths from two sets of modeling with two different quality of life instruments: gQoL and QoLS-N.](image-url)

**Figure 5** Comparison of significant a) cross-lagged and b) simultaneous paths from two sets of modeling with two different quality of life instruments: gQoL and QoLS-N. Figure 5 summarizes only the statistically significant paths observed between General Health and overall Quality of Life, indicated as arrows in the direction of causality. The causal paths are labeled with their corresponding QoL instrument and standardized regression coefficients derived from structural equations. Paths within each concept from one time-point to another, for example from General Health at three months to General Health at 12 months, are not drawn. See Table 3 for model fit indices, and Additional files 1 through 4 for separate model parameters.
ing of assessments as more or less sensitive to the causal paths investigated.

**Conclusion**
Unidirectional models of causality are inadequate to explain the effect of cardiac surgery on overall QoL. Overall quality of life can causally influence as well as be an outcome of health status after coronary artery bypass surgery. Our analysis substantiates the potential for reciprocal effects within the Wilson and Cleary model. This study offers a pilot design for confirmatory modeling with more frequent sampling of a larger patient population.

**Abbreviations**
- gQoL: Single-item Global Quality of Life question
- QoL: Quality of Life
- QoLS-N: Quality of Life Survey-Norwegian
- SF-36 GH: Short Form 36 General Health subscale

**Competing interests**
The author(s) declare that they have no competing interests.

**Authors’ contributions**
LM initiated this paper as part of a larger study of patient reported outcomes and drafted the manuscript together with MV, who provided statistical advice. MA participated in data collection. All authors critiqued revisions of the paper and approved the final manuscript. EF, BRH and AKW supervised LM and MA; EF was principal investigator for the research program on off-pump versus on-pump coronary artery bypass surgery.

**Additional material**

**Additional file 1**
Cross-lagged model with Global Quality of Life (gQOL) displaying unstandardized and standardized estimates, together with correlation coefficients between error variances.
Click here for file

**Additional file 2**
Simultaneous reciprocal effects model with Global Quality of Life (gQOL) displaying unstandardized and standardized estimates.
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[http://www.biomedcentral.com/content/full/1477-7525-5-27-S2.pdf](http://www.biomedcentral.com/content/full/1477-7525-5-27-S2.pdf)

**Additional file 3**
Cross-lagged model with Quality of Life Scale – Norwegian version (QOLS-N) displaying unstandardized and standardized estimates, together with correlation coefficients between error variances.
Click here for file

**Additional file 4**
Simultaneous reciprocal effects model with Quality of Life Scale – Norwegian version (QOLS-N) displaying unstandardized and standardized estimates.
Click here for file

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**References**


