A prospective follow-up study of chest pain patients - with emphasis on patients with panic disorder.

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Preface

The present thesis is based on the papers listed below, referred to in the text by their Roman numbers in brackets.

List of papers:

I. Dammen T, Bringager CB, Arnesen H, Ekeberg O, Friis S.” A 1-year follow-up study of chest-pain patients with and without panic disorder”. Gen Hosp Psychiatry 2006; 28(6):516-524.

II. Bringager CB, Friis S, Arnesen H, Dammen T. “Nine year follow-up of panic disorder in chest pain patients: Clinical course and predictors of outcome”. Psychosomatic Medicine. Submitted.

III. Bringager CB, Husebye T, Friis S, Arnesen H, Dammen T. “A long-term follow-up study of chest pain patients: Effect of panic disorder on mortality, morbidity and quality of life”. Cardiology. In Press.

IV. Bringager CB, Dammen T, Friis S.”Nonfearful panic disorder in chest pain patients”. Psychosomatics 2004; 45:69-79

V. Bringager CB, Gauer K, Arnesen H, Friis S, Dammen T. ”Nonfearful panic disorder in chest pain patients: Status after nine-year follow-up”. Psychosomatics. In press.

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Abbreviations

ACQ	Agoraphobic Cognitions Questionnaire
ANOVA	Analysis of variance
B	Beta
BMI	Body mass index
CAD	Coronary artery disease
CABG	Coronary artery by-pass grafting
CBB	Christine Bull Bringager
CI	Confidence interval
DSM-IV	Diagnostic and Statistical manual of Mental Disorders, 4th edition
DSM-III-R	Diagnostic and Statistical manual of Mental Disorders, 3rd edition, revised
D(u)	Observed number of deaths in the study sample
ECG	Electrocardiography
ED	Emergency department
EPQ	Eysenck Personality Questionnaire
GAD	Generalized anxiety disorder
HARP	Harvard-Brown Anxiety Research Project
HRV	Heart rate variability
IAS	Illness Attitude Scale
HRQOL	Health related quality of life
MIA	Mobility Inventory for Agoraphobia
MOS SF-36	The Medical Outcomes Study Short Form-36
NCCP	Non-cardiac chest pain
NFPD	Nonfearful panic disorder
NoPD	No panic disorder
Non-PD	No panic disorder
OR	Odds ratio
PD	Panic disorder
PDQ	Personality Diagnostic Questionnaire
PCI	Percutanous coronary intervention
RR	Relative risk
SCID-I	Structured Clinical Interview for DSM-IV- Axis I disorders
SCL-90-R	Symptom Checklist-90-Revised
SD	Standard deviation
SF MPQ	Short Form McGills Pain Questionnaire
SMR	Standardized mortality ratio
SPSS	Statistical Package for Social Sciences
TAS-20	The 20-itemToronto Alexithymia Scale
TD	Toril Dammen
VAS	Visual Analogue Scale

Introduction

1.1.0 Chest pain

1.1.1. Chest pain epidemiology and etiology

Chest pain is a common symptom in the general population. According to a population-based study, the lifetime prevalence of chest pain is approximately 39% and 33% have non-cardiac chest pain (NCCP) (i.e. not diagnosed as ischemic heart disease or not classified as angina according to the Rose Angina Questionnaire criteria: substernal pain precipitated by exertion and relieved by rest) (1). About 23% of patients with non-cardiac chest pain visit a doctor because of this symptom and male sex, increasing age, mild symptoms and anxiety are associated with health care seeking (1). Moreover, 12% suffer from chronic chest pain which is the most common reason for referral to cardiac outpatient clinics (2;3).

In about 50% of chest pain patients referred to cardiology clinics there is no evidence of coronary artery disease (4). Still, chest pain patients often go through costly and time-consuming investigations that put an economic burden on the health care system (5). Heart related disorders like micro vascular ischemia and mitral valve prolapse are suggested to be causes of chest pain in a minority of patients, despite normal angiograms (6). Gastro-esophageal disorders, especially esophageal reflux, are thought to explain the symptoms in about 30% of cases. Additionally, musculoskeletal disorders, pulmonary disorders, other gastrointestinal disorders and psychiatric disorders (major depression, anxiety disorders and somatoform disorders) are also reported as non-cardiac causes of chest pain (3;5-10).

Panic disorder (PD) is the anxiety disorder most frequently associated with chest pain as it occurs in 10 to 60 % of chest pain patients with or without coronary artery disease in cardiology clinics or emergency departments (11-14). Cross sectional studies of PD in chest pain patients have reported associations with high psychological distress, high rates of co-morbid psychiatric disorders, suicidal ideation, work disability, quality of life impairment and high medical utilization (12-14). However, there is a lack of longitudinal studies of chest pain patients with PD. To the best of our knowledge there are only two previous studies (15;16) which both have major shortcomings as described in section 1.2.3. One of the main purposes of the present study was therefore to explore the longitudinal course of PD and the effect of PD on the short and long-term outcome of chest pain patients (papers I-III).

1.1.2. Prognosis of chest pain patients.

The results of studies on mortality in chest pain patients are somewhat inconsistent. Most studies investigating the relationship between NCCP and cardiac morbidity and mortality, are conducted with NCCP patients with negative coronary angiography. These studies have reported an excellent mortality prognosis with survival rates of 91-98% up to 12 years after the angiographic assessments (17-19). In contrast, two population-based studies reported that the mortality rate of chest pain patients is higher than that of the normal population. One of these studies concerned men with "possible angina", which was detected using the World Health Organization's Angina Questionnaire, and normal exercise test (20). The other concerned men with non-specific chest pain that was not considered typical of angina (21). Both studies reported a significantly greater incidence of cardiovascular mortality in patients with chest pain than in those with no symptoms of angina after 26 and 16 years respectively (RR 1.97-2.46).

Despite the excellent prognosis regarding mortality and risk of developing cardiac disorder in patients with negative angiography, as much as 70% of the patients still have regular chest pain at follow up 1-11 years after cardiac investigation (18;22-24) and about 50% continue to believe they have a heart condition (24;25). Many (71-79%) are continuously treated as having a heart condition by their physicians by prescribing heart medication (18;25). Additionally, NCCP patients report physical and social disability and it has been reported that 50% are unable to work at follow-up (24).

The reason why these patients have such a poor prognosis is largely unexplored. Despite the high prevalence of PD in chest pain patients, there is a scarcity of research addressing the association between the presence of PD and the long-term outcome of these patients.

1.2.0. Panic disorder

Panic disorder is characterized by recurrent panic attacks followed by anticipatory anxiety or avoidance behavior which interfere with the patients work, family and social life. The panic attacks are unexpected and consists of at lest four of 13 somatic or cognitive symptoms: palpitations, sweating, trembling, shortness of breath, choking, chest pain, nausea, dizziness, derealization or depersonalization, paresthesias, chills or flushes, fear of dying, fear of going crazy or losing control. The DSM IV criteria for PD are shown in table 1. There is evidence that the age of onset of PD is bimodal (26). The majority have their first panic attack in the twentieths (27) but there is also a group with age of onset between age 50 and 60 (late-onset panic disorder) (26;28;29). It is well documented that PD is associated with physical and

social disability, occupational dysfunction, quality of life impairment and health care utilization in psychiatric and primary care patients (30-33).

1.2.1. Prevalence of panic disorder

According to the US National Co morbidity Survey Replication, the lifetime prevalence of PD in the general population is estimated to 4.7% and the 12 month prevalence to 2.8 % (27). Furthermore, 3 to 8 % of patients seen by primary care physicians suffer from PD (34). The rate of PD is considerably higher in patients who present with symptoms unexplained by a medical disorder. Studies have reported the following prevalence's of PD in patients with various conditions; irritable bowel syndrome (29-38%), medically unexplained dizziness (13%) and chronic fatigue (13-30%) (35). Among chest pain patients the prevalence of PD is estimated to 25-60% among those with NCCP (11;36) and 10-50% among those with coronary artery disease (CAD) (37). The rather large divergence in prevalence is due to differences in settings (i.e. family practice, emergency or cardiology departments) and chest pain characteristics (i.e. typical vs. atypical chest pain).

1.2.2. Panic disorder and chest pain.

Chest pain is one of the symptoms included in the list of diagnostic criteria for panic attacks and 22-70% of PD patients experience chest pain as one of the symptoms of an attack (38). PD patients often relate their chest pain to heart disease (39) even after CAD is ruled out by angiography (15). The fear of having heart disease causes frequent referral to emergency departments or cardiology clinics with costly cardiological investigations as the result (11;33;35).

Efforts have been made to discriminate between chest pain associated with either PD or CAD. In PD patients the chest pain is more often atypical as opposed to CAD patients who have more typical chest pain (defined as substernal, exertional and relieved by nitroglycerine) (11). However, PD patients may also have typical chest pain and panic attacks may in fact cause cardiac ischemia in patients with coronary artery disease (40). In a considerable proportion of chest pain patients PD and CAD co-exist (11;37). Therefore, it is difficult to exclude one diagnosis or the other just by clinical judgment. Subsequently Katerndahl proposed that when either CAD or PD is recognized by a primary care physician, the other should also be considered (11).

1.2.3. Outcome of panic disorder in chest pain patients.

The outcome of panic disorder in chest pain patients have been reported in two previous follow-up studies. Beitman and colleagues (15) investigated the outcome after three years of 72 patients with chest pain and negative coronary angiography of whom 36 suffered from PD. They found an association between PD at baseline and prevalence of chest-pain episodes at follow-up. PD patients were more convinced that their symptoms were heart-related and rated themselves as more disabled at follow-up compared to the patients without PD. Fleet and colleagues (16) conducted a two-year follow-up of chest pain patients admitted to an emergency department and reported higher chest pain prevalence and medical utilization among the patients with PD. Furthermore, the PD patients were more impaired at follow-up regarding panic-anxiety symptoms, agoraphobic avoidance, and reported more frequently poor general health and suicidal ideation (32%).

However, these studies are limited by small sample size (n=72) (15), low-participation rate at follow-up (54%) (16) and lack of diagnostic reassessments (15;16) regarding PD and CAD. Therefore the outcome of PD in patients presenting with chest pain presenting in cardiology clinics is largely unexplored.

1.2.4. Outcome of panic disorder in psychiatric settings.

Course of panic disorder

A methodological challenge with research addressing the course of PD is that there is no consensus with regard to criteria for remission and relapse. In 1994 a conference report was published making recommendations on standardized assessments for panic disorder research (41). However, the group was unable to come to an agreement regarding definitions of "remission", "recovery" and "relapse". Therefore, studies of PD have used different criteria for remission which make comparisons difficult.

In the Harvard Brown Anxiety Research Project (HARP) (42), the intensity of panic attacks and agoraphobia was graded on a rating scale from one to six where one indicated a symptom free state and six indicated daily panic attacks or extensive phobic avoidance. Full remittance of PD was defined as eight consecutive weeks of symptom ratings "one" or "two" for both panic and agoraphobia. Relapse was defined as one week of rating "five" or more after a period of remittance. The HARP study included PD patients (n=309) admitted to one of 11 anxiety disorder clinics in the Massachusetts area who were followed monthly for two years. They reported a chronic course of PD with high risk of relapse after remission of PD symptoms (42). After 12 years, the probability of remission was 82% for patients with PD without

agoraphobia and 48% for patients with PD with agoraphobia, but the probability of recurrence after a period of remission was more than 50% for both groups (43).

Katschnig and colleagues (44) included PD patients (n=1647) who were recruited from psychiatric clinics and through news media to participate in clinical drug trials (The Cross-National Collaborative Panic Study Phase I or II). They did not use criteria for remission and relapse of PD, but reported the panic attack frequency during the week and month preceding the follow-up interview by using the Panic Attack Scale. In addition, global phobia was rated on an 11-point scale. Four years after the end of the trials 25% of the patients were reassessed (45) and the authors reported subgroups of PD courses where 31% remitted and stayed well, 24% had a fluctuating course and 45% had a more chronic debilitating course. Furthermore, cohorts of participants of this study have been reassessed after six, 11 and 15 years (46-48). After six years and 11 years 75% and 87.5% reported no panic attacks while after 15 years 18% still met criteria for current PD according to DSM III.

The results of follow-up studies of PD patients referred to psychiatric treatment may not be generalized to PD patients seen in other medical settings as there is some evidence that few PD patients in medical settings receive effective anti-panic medication or psychotherapy (15;49;50). Because the follow-up studies of PD in chest pain patients have not made diagnostic reassessments, the stability of PD among these patients is unexplored.

Outcome of panic disorder.

Symptoms of anxiety and phobic avoidance. Although many patients do not fulfill criteria for PD at follow-up and the majority of patients improve regarding symptoms of anxiety and phobic avoidance, few are symptom-free (44;51). Moreover, residual anxiety and avoidance symptoms are of negative prognostic significance for panic relapse (52). The knowledge regarding symptom reduction/persistence in PD is derived from studies of patients who have received antipanic medication or psychotherapy. In addition, a substantial proportion of patients still use medication at the time of follow-up, therefore the true natural course of symptoms is unknown.

Psychiatric co-morbidity. One cross-sectional study (53) reported that 61% of patients referred for treatment of PD suffer from at least one other anxiety or affective disorder, but the overall co-morbidity decreased when PD was treated. A recent epidemiological study (27) reported that 83% of PD patients without agoraphobia and 100% of PD patients with agoraphobia suffered from at least one other psychiatric disorder and agoraphobia was found in about one fourth of patients with lifetime PD. Co-existence of agoraphobia and PD is far

higher in patients seen in psychiatric clinics (75-80%) (32;44;54). One study reported that agoraphobia is less readily treated than panic attacks (55) but still tend to decrease over time (44;46). Agoraphobia is most commonly viewed as a consequence of panic attacks, but it may also precede the onset of attacks (52). The rate of co-morbid generalized anxiety disorder (GAD) is also significant and in some cases GAD may rather be secondary to panic symptomatology (53;54). In those cases, GAD symptoms may diminish when PD is treated (53). Otherwise, GAD generally has a more chronic and persistent course than PD (43). Regarding major depression, about 60% of PD patients experience one or more depressive episode during the lifetime course of their illness while about 30% of PD patients have experienced a depressive episode during the last year (56). The rate of major depression and alcoholism tend to increase over time in some follow-up studies of PD (47), yet, not in all (46). The change in co-morbidity between PD and other psychiatric disorders over time has not been addressed in previous studies of PD in chest pain patients.

Suicidal ideations and attempts. Recent research have revealed panic disorder as an independent risk factor for suicidal ideation in primary care patients (57); and a prospective population based study reported anxiety disorders, and among them PD, as risk factors for future suicidal ideation and attempts (58) when co-morbid disorders were controlled for. There is also some evidence that suicidal ideation increases over time in chest pain patients with PD (16), but the long-term association between PD and suicidal ideation in chest pain patients is unknown.

Quality of life. The association between PD and quality of life impairment has been established in several cross-sectional studies of PD patients in community samples (59;60) and in psychiatric settings (31;61). Health related quality of life (HRQOL) is one of the targets for treatment of PD (62), but with some exceptions, the longitudinal outcome of PD patients with regard to HRQOL has hardly been addressed. Previous studies have used the Sheehan Disability Scale to assess quality of life of PD patients. Katschnig et al.(63) reported a significant improvement in disability of three life domains. After four years the proportions of patients reporting no or mild disability was 82% regarding work, 77% regarding family life and 70 % regarding social life while the proportions at baseline were 22%, 19% and 7% respectively. Carpinello et al. (32), came to the opposite conclusion as they reported significant disability in 60% of their PD patients and 40% were dissatisfied with at least 50% of life domains. These discrepancies may be explained by the naturalistic design of the studies. Furthermore, two studies have used HRQOL measurements to evaluate treatment outcome of PD. They have reported significant short-term (six weeks and 16 weeks) improvement in

quality of life measured by the MOS Short Form 36 in clonazepam (64) and imipramin (65) treated patients. However, no previous research has addressed the outcome of PD in chest pain patients in terms of HRQOL impairment.

1.2.5. Predictors of panic disorder outcome.

The majority of studies that have attempted to establish predictors of PD outcome have focused on factors that affect PD remission or relapse of PD symptoms after a period of remission. The results have been somewhat inconsistent which may be explained by the use of different remission criteria and varying lengths of follow-up (two to eight years). Co-morbid agoraphobia has in most follow-up studies of PD predicted decreased likelihood of PD remission (43;66;67). One study reported that co-morbid major depression decreased the likelihood of remission from PD with agoraphobia but not of PD without agoraphobia, but it increased the odds of relapse of both types of PD (43). Other studies have not found an association between major depression and time to PD remission (66;67). Moreover, presence of personality disorders decreased the probability of achieving a period of PD remission in one study (67) but not in another (68). Co-morbid anxiety disorders have also been associated with a decreased remission rate (67). Regarding demographic variables, women tend to be more likely to remit than men, but their relapse rate was three-fold higher (69). Low socioeconomic status has also predicted longer time to remission from PD (66). Furthermore, in one study disability at baseline was the only variable that predicted disability at four year follow-up (63).

These studies have been conducted in PD patients in clinical or research settings and no previous study of chest pain patients with PD have focused on predictors of PD outcome. Such knowledge is of crucial importance when deciding which patients are in greatest need of treatment.

1.2.6. Treatment of PD

In a recent meta-analysis of PD treatment, a combination of psychotherapy (21 of 23 studies used behavioral or cognitive behavioral therapy) and anti-depressants or psychotherapy alone were recommended as first choice of treatment (70). According to recommendations based on proceedings from the World Council of Anxiety meeting in 2001(71), the first choice of medical treatment for PD is selective serotonin reuptake inhibitors, but high-potency benzodiazepines, reversible monoamine oxidase inhibitors and tricyclic antidepressants are also efficient. The recommended treatment length is 12 to 24 months and for some patients the treatment should be life-long (71;72).

Despite specific and well-documented treatment recommendations, a recent epidemiological study of PD reported that only about 40% of PD patients receive treatment meeting published treatment guidelines (27). Among PD patients in primary care or cardiology settings the rate of treatment of PD is even lower. Cross-sectional studies have reported that 28% of PD patients in primary care received pharmacological antipanic treatment and 12% received cognitive therapy (49;50), while amongst chest-pain patients with PD less than 10% received antipanic treatment (14). A previously reported hypothesis regarding low rates of PD treatment in chest pain patients, is that the PD patients are often unrecognized (13). However, in two follow-up studies of PD in chest pain patients, only 22% (16) and 33% (15) received some kind of PD treatment even though PD was identified. Because treatment may affect PD outcome it is necessary to record it in follow-up studies.

1.2.7. Panic disorder and cardiac morbidity and mortality.

Previous studies have suggested that there is an association between PD, cardiovascular mortality, and CAD (73;74). In the 1980's, Coryell and colleagues (75;76) reported an increased risk of cardiovascular deaths among inpatients and outpatients with 'anxiety neurosis'. However, the number of deaths in these studies were low (six and four respectively) and systematic psychiatric diagnostic assessments and causes of death were lacking. Furthermore, some epidemiological studies have reported a significant association between sudden cardiac death and self-reported panic-like symptoms in healthy men and women (77-81). One hypothesis attributes a possible link between PD and CAD to an elevated incidence of risk factors for CAD in PD patients (11;82). Another hypothesis emphasizes decreased heart rate variability in PD patients which increases the risk of ventricular arrhythmias and sudden cardiac death (83). However, an extensive review published in 1998 concluded that studies of associations between PD, CAD, and cardiovascular mortality suffer from serious methodological limitations, such as the lack of sound methodological assessment of PD and prospective design (84). Since then, a recently published cohort study of nearly 40.000 persons diagnosed with PD reported that having a PD diagnosis almost doubled the risk for subsequent CAD (85).

Yet, the association between PD and cardiac morbidity and mortality is controversial and this association has not previously been addressed in prospective follow-up studies of chest pain patients.

1.3.0. Nonfearful panic disorder

Nonfearful panic disorder (NFPD) is a type of PD that was first described by Beitman and colleagues (86) in 1987 among cardiology patients who had panic attacks without the experience of fear. These patients met the DSM III-R criteria for PD by reporting attacks of intense discomfort and at least four of the twelve remaining symptoms on the screening checklist, but they did not report subjective free floating anxiety or fear of dying, fear of 'going crazy', or doing something uncontrolled.

Three previous studies in cardiology and emergency department settings have estimated the prevalence of NFPD to 32–44% among PD patients (86-88). However, the concept of NFPD is somewhat controversial. It is not a DSM-IV illness and it remains equivocal whether NFPD is a subgroup of PD or whether it is a distinct diagnostic entity (88;89). Questions have also been raised as to whether NFPD may be better classified as a somatoform disorder, or whether NFPD patients have an undetected medical disorder that is wrongly identified as NFPD (88). Moreover, alexithymia (not having words to express feelings) has been proposed as a possible explanation for NFPD symptoms (90).

To establish NFPD as a well-defined panic disorder subtype would aid its accurate recognition and make an incentive for treatment. So far, it seems reasonable to regard NFPD as a variety of PD based upon cross-sectional comparisons including one longitudinal study suggesting that NFPD is highly similar to PD with fear (86-88;91). One study has found that NFPD patients respond similarly to PD patients to lactate infusions and treatment with anxiolytic medication (92).

Still, more research is required to confirm the validity of NFPD as a subtype of PD. The results of previous studies of NFPD need to be replicated in other PD samples and data regarding the predictive validity of NFPD are currently inadequate (i.e. regarding long-term course). One previous study has addressed the two-year course of NFPD but lacks diagnostic reassessment of PD and NFPD(88).

Aims of the study

The primary aim of the study was to investigate the prognosis of chest pain patients when they are encountered in a cardiology outpatient clinic with special emphasis on the importance of panic disorder:

2.1. Prevalence of panic disorder at follow-up (Papers I and II).

(1) Estimate the prevalence of PD after one year and after nine years among chest pain patients diagnosed with PD at the first examination.

2.2. Outcome of baseline panic disorder at follow-up (Papers I-III).

(1) Compare the patients with and without PD at baseline regarding co-morbid psychiatric disorder, psychological distress, panic-anxiety symptoms, suicidal ideation, hypochondriacal features and health related quality of life after one year and after nine years.

(2) Compare the patients with and without panic disorder at baseline regarding change in scores of the outcome measures outlined above from the first examination to follow-up after one and after nine years.

(3) Compare patients with persistent PD after nine years to those with PD in remission regarding outcome measures listed above.

2.3. Predictors of having persistent PD at follow-up (Paper II).

(1) Identify predictors of having PD after nine years among those with PD at the first examination.

2.5. Treatment and perceived treatment need of PD patients (Papers I and II).

(1) Describe the current PD treatment at follow-up after one year and after nine years and describe the perceived need for treatment after one year.

2.4. Effect of PD on chest pain, CAD and mortality (Papers I and III).

(1) Compare the PD and NoPD patients regarding persistent chest pain.

(2) Compare the death rate in the present sample to that of the general population.

(3) Compare PD and NoPD patients regarding cardiac events, risk factors for CAD and mortality.

2.6. Prevalence and outcome of nonfearful panic disorder (NFPD) in chest pain patients (Papers IV and V).

(1) Estimate the prevalence of NFPD at baseline and after nine years among the PD patients.

(2) Compare the patients with NFPD to those with PD with fear and those without PD regarding demographic characteristics, co-morbid psychiatric disorders, somatic disorders, chest pain, psychological distress, alexithymia, health care utilization and health related quality of life at baseline and after nine years.

Material and methods

3.1. Patient sample

3.1.1. Baseline

Between December 1994 and November 1996, 301 patients consecutively referred to one of four cardiology outpatient clinics in Oslo, Norway were asked to participate in an explorative study of psychological factors in chest pain patients. The patients had to meet the following inclusion criteria: 1) referred for investigation of chest pain as their main complaint; 2) no documented history of organic heart disease; 3) age 18–65 years; 4) no psychosis; 5) able to understand and write the Norwegian language; and 6) signed the informed consent form. Documented organic heart disease included: a) previous myocardial infarction verified by ECG changes or enzyme examination, b) previous positive exercise test, thallium scintigraphy or coronary angiography, c) mitral valve prolapse verified by auscultation and echocardiography and d) arrhythmia documented by ECG.

Of the 264 patients who met the inclusion criteria, 199 agreed to participate in the study and these patients also constitute the baseline participants of the present study. There were no significant difference between participants (N=199) and non-participants (N=65) in terms of age, sex, coronary artery disease risk factors or prevalence of other medical disorder. The participants were diagnosed with coronary artery disease more often than the non-participants (16.1% vs. 3.1%; P=0.005). Of the 199 participants, 49 % were women and the mean age was 50,4 years (SD 9,4), 32 patients (16.1%) were diagnosed with coronary artery disease and 76 patients (38.2%) were diagnosed with panic disorder at baseline. Seven patients had both diagnoses (14).

3.1.2. One year follow-up

After one year, all study participants were asked to take part in a follow-up study. One patient had died and one patient had suffered a major stroke which made her ineligible. Of the 197 patients eligible for follow-up, 152 completed both the structured psychiatric interview and self-report questionnaires, 12 completed only self-report questionnaires and one completed the interview only. Thus, the participation rate was 77.2% (152/197) regarding complete data and 83.8% (165/197) regarding complete and incomplete data. Thirty-two patients did not participate in the follow-up study for the following reasons: Various disease states (n=4),

having moved to another part of the country or abroad (n=5), did not have time (n=1), or unknown reasons (n=22). We checked the Norwegian National Population Register for those who did not respond to any contact, but found no registered deaths.

3.1.3 Nine year follow-up

Eight to ten years after the baseline study, the participants were invited to a second follow-up. Fourteen patients had died and one had suffered a major stroke. Of the 184 eligible patients 150 participated in the follow-up study (82%). Of the 34 non-participants, seven had left the country, 12 could not be located, and 12 patients did not participate for the following reasons: Study not relevant to their condition at the time (n = 4), did not have time (n = 4), too difficult to come to the hospital (n = 1), afraid of giving away sensitive information (n = 1), disappointed with previous treatment at the hospital (n = 1), and unknown (n = 1). Three patients who filled in questionnaires did not attend psychiatric or cardiological evaluation sessions and were considered non-participants. Of the 150 participating patients, 12 attended the psychiatric evaluation session but not the cardiological evaluation session, which was scheduled to take place about a week after the psychiatric evaluation session. The reasons for their absence are unknown. They were still considered participants because information about their previous cardiac disorders could be obtained from their medical records.

3.2.0 Methods

3.2.1. Assessments of sampling bias

Using baseline data, the participating patients at the one-year and nine-year follow-up were compared to the non-participants to evaluate whether subject loss was systematic.

Regarding the one-year follow-up, the patients with complete data (n = 152) were compared to those who did not meet to the one-year follow-up or had incomplete data (n = 45). The participating patients were significantly older than the non-participating patients (mean age 51.8 $\pm$ 8.7 years vs. 46.2 $\pm$ 10.5 years; $P < 0.001$). Otherwise, there were no significant differences between participants and non-participants regarding gender, prevalence of CAD, psychiatric disorders or scores on any outcome variable.

Regarding the nine-year follow-up, when assessing sampling bias among the eligible patients, there were no significant differences between the 150 participants and the 34 non-participants regarding sex, age, years of education or income at baseline. The participants did

not differ significantly from non-participants in prevalence of CAD (12% vs. 17%, respectively), PD (41% vs. 38%, respectively), or any of the outcome variables. We also compared the participants to the 15 non-eligible patients and found that the latter group were older mean age 50.1 ± 8.9 years vs. 55.0 ± 7.7 years; P=0.066) and had lower SF-36 scores (i.e. more HRQOL impairment) although it reached statistical significance regarding the physical functioning subscale only (mean 78.5± 18.9 vs. 66.1±19.7; P=0.018). They had also significantly higher baseline SCL-90 somatization scores (mean 1.0 ± 0.7 vs. mean 1.5 ± 0.8; P=0.033).

3.2.2. Procedure

The 197 patients eligible after one year were mailed a letter with an invitation to participate in a follow-up study, which comprised an appointment with a psychiatrist (TD), who had also conducted the baseline interviews, for the purpose of assessing psychiatric diagnosis and completing self-report questionnaires. The mean period between the cardiac outpatient investigation and the one-year follow-up was 12.3 months (range = 10.4–16.6, *SD* =1.1).

From December 2003 to September 2005 the Norwegian National Population Register was searched for deaths among the baseline participants and the 184 eligible patients were mailed a letter with an invitation to participate in a long-term follow-up study. The invitation included details of an appointment with an experienced psychiatric resident trained in psychiatric interviewing (CBB), and an appointment for a cardiological evaluation at the outpatient clinic of the Department of Cardiology, Ullevål University Hospital. The mean time between the baseline investigation and the long-term follow-up was 8.6 years (range=8.1-9.9, SD = 0.35).

Data on non-fatal myocardial infarctions, percutaneous coronary interventions (PCI), and coronary artery bypass grafting (CABG) for the 12 participants who did not attend the cardiological evaluation and the 34 non-participating patients were obtained from their medical records. The causes of death of the 14 deceased patients were obtained from the National Death Register. The death rate in the study population was compared to the death rate calculated by Statistics Norway for a Norwegian population of equal age and gender distribution.

3.2.3. Psychiatric assessments

Psychiatric interview

Psychiatric disorders were assessed by using the Structured Clinical Interview for DSM IV- axis I disorders (SCID-I) (93) at baseline and at both follow-up investigations. The interview assesses current psychiatric state disorders (i.e. diagnostic criteria met within one month before interview) and lifetime psychiatric state disorders (i.e. diagnostic criteria met previously, but not last month). It was carried out by a psychiatrist, who is a trained interviewer (TD) at baseline and one year follow-up and by an experienced psychiatric resident (CBB) at the nine year follow-up. When a cardiological investigation was scheduled, the psychiatric interview was conducted before the cardiological appointment to ensure that the patients and the psychiatrist were blind to the results of the cardiologists. The psychiatrists were also blind to previous psychiatric diagnosis at the follow-up assessments. PD was recorded as current (diagnostic criteria met within one month before the interview) or in remission including PD in partial remission (diagnostic criteria met within the last 6 months prior to the interview, but not last month and only few symptoms of PD present) and PD in full remission (diagnostic criteria met previously, but not within the last six months and no symptoms of PD present). Major depression was recorded as current or lifetime, and the other diagnoses as current. The diagnoses were recorded immediately after the interviews. All interviews were audiotaped at both baseline and follow-up investigations. Thirty-five randomly selected tapes from baseline and twenty interviews from the one-year follow-up were assessed by an experienced psychologist who was blind to the scores the interviewer had assigned. Thirty-two randomly selected tapes from the nine-year follow-up were assessed by TD who conducted the previous interviews. The interrater reliability scores were estimated for the diagnoses of panic disorder, major depression, generalized anxiety disorder, and somatoform pain disorder. The interrater reliability scores ranged from good to excellent for these psychiatric diagnoses at both baseline and follow-up (kappa 0.69–1.0). The kappa for panic disorder at the three evaluations was 0.88, 1.00 and 1.00 respectively.

Self-report measures

Demographic variables.

A self-report questionnaire comprising sex, age, marital status, education, work-status and income was filled in by all patients at baseline and reviewed by the investigator during the interview. At the follow-up interviews the patients were reassessed regarding marital and work status.

Psychological distress.

Symptom Checklist-90-Revised (SCL-90-R) (94) is a 90 item self-report questionnaire covering questions about a wide variety of psychological symptoms which are rated on a five point scale from 0 to 4 according to the level of experienced distress during the last week. The items generate nine dimensions: anxiety, phobic anxiety, depression, somatization, obsessiveness, psychotisism, paranoididity, interpersonal sensitivity and hostility. The anxiety, depression and somatization subscales were considered most relevant and were therefore used in the baseline and follow-up investigations (14).

Suicidal ideation

Suicidal ideation was assessed by the SCL-90-R item 15: "During the last 7 days, how much were you distressed by thoughts of ending your life?" The responses were categorized as "0 = *no thoughts*" and all other responses as "1 = *suicidal thoughts*").

Panic-Agoraphobia symptoms

Agoraphobic Cognitions Questionnaire (ACQ) (95) is a 20 item questionnaire which assesses beliefs about negative consequences of experiencing anxiety. The frequency of each belief is rated on a five point scale graded from 1=" The thought never occurs when I am anxious" to 5= "The thought always occurs when I am anxious". ACQ was applied at baseline and at the long-term follow-up study.

Mobility Inventory for Agoraphobia (MIA) (96) contains 24 agoraphobic situations which are rated according to how often they are avoided on a five point scale from 1="never avoided" to 5="always avoided". The situations are rated both as if they were encountered alone and as if they were encountered accompanied. MIA was applied at baseline and at the long-term follow-up study.

Hypochondriacal features.

Illness Attitude Scale (IAS) (97;98) is a 29 item self-report questionnaire rated on a five-point scale from 0 to 4 measuring health beliefs associated with hypochondriasis and attitudes

towards disease. Originally the scale comprised eight subscales. However, validations studies applying the scale to different medical patient samples have reported that the scale rather comprises two psychometrically sound subscales: Health Anxiety and Illness Behavior (95;99) which were used in the present study.

Symptom attribution

At baseline and after one year the patients were asked what they considered to be the cause of their chest pain. Cardiac disease, gastrointestinal disease, muscelo-skeletal disorder and psychological factors/stress were each rated on a global seven point scale from 1 = "not at all" to 7 = "very high degree".

Health related quality of life

The Medical Outcome Studies Short Form 36 (SF-36)(100) is a 36 item self-report questionnaire which generates eight subscales: physical functioning, role limitation due to reduced physical functioning, general health, vitality, body pain, social functioning, mental health and role limitation due to emotional problems. The subscales are calculated from the SF-36 raw scores by use of a transformation manual which yield subscale scores with values from 0 to 100. A lower score indicate poorer quality of life. The scores decrease with increasing age, female gender and lower income (101). A psychometrically sound and validated Norwegian translation of the SF-36 was used in the present study (102).

Personality disorders.

The Personality Diagnostic Questionnaire for DSM-IV (PDQ-4) (103) is designed to assess ten personality disorders (paranoid, schizoid, schizotypal, histrionic, narcissistic, antisocial, borderline, avoidant, dependent and obsessive-compulsive) included in DSM-IV. The items assessing antisocial personality traits were omitted because some patients reported that they found the questions offensive. Thus, a 97 "true/false" item PDQ version was applied at baseline and used in the long-term follow-up study to assess predictors of still having PD after nine years among the baseline PD patients. At follow-up the following variables derived from PDQ were used: A total PDQ score and a diagnosis of the each of the personality disorders with a prevalence above 10% (avoidant (14%), depressive (14%), obsessive (27%) and paranoid (15%)).

Neuroticism

The neuroticism subscale of Eysenck Personality Questionnaire (EPQ)(104) was applied at baseline and used in the long term follow-up study to assess predictors of still having PD after nine years among PD patients. It comprises 23 "yes/no" items.

Alexithymia

Toronto Alexithymia Scale- 20 item version (TAS-20) (105) is a 20 item questionnaire that was applied at baseline to assess alexithymic features such as difficulties identifying and describing feelings and externally oriented thinking. It derives a TAS-20 total score and individuals scoring ≥ 61 are considered alexithymic while individuals scoring ≤ 51 are non-alexithymic. It was used in the first study of NFPD (paper IV)

Health care utilization and use of medication.

The use of medical facilities was assessed by the following questions: (1) "During the last 12 months have you contacted a health care provider because of chest pain? Yes/No"; (2) "If yes, indicate number of hospitalizations, emergency department visits, and visits at general practitioner, medical specialist, psychiatrist/psychologist and physiotherapist because of chest pain"; (3) "During the last 12 months have you contacted a health care provider because of other symptoms or diseases? Yes/No"; (4) "If yes, indicate number of hospitalizations, emergency department visits, and visits at general practitioner, medical specialist, psychiatrist/psychologist and physiotherapist because of other symptoms or diseases". The patients were also asked to list current use of medication.

Perceived treatment need.

Patients diagnosed with PD at the one year follow-up were asked if they received any current PD treatment, whether they experienced a need for treatment of PD symptoms, and if they wanted a report including information on PD, and general treatment recommendations to be sent to their GP.

Chest pain

At the follow-up investigations a self-designed chest-pain form was applied that included the following: (1) Chest pain remission ("Has your chest pain totally disappeared, meaning you have not had chest pain during the last four weeks? Yes/no"); (2) Experience of change in chest pain since baseline (0 = *no chest pain,* 1 = *better,* 2 = *no change,* 3 = *worse*); (3)

Perceived explanation of chest pain ("Did you get any explanation of chest pain? Yes/no"); (4) Degree to which patients' perceived the explanation of chest pain to be sufficient (1 = *not at all,* 7 = *very high degree*). At the one-year follow-up study the form also included aspects of illness perceptions: (a) Perception of future (6 months) outcome of chest pain (0 = *no pain*, 7 = *much worse*); (b) What the patient can do to control the chest pain (1 = *nothing*, 6 = *a lot*); (c) What health personnel, such as doctors, can do to control the chest pain (1 = *nothing*, 6 = *a lot*).

Short Form McGill Pain Questionnaire (SF-MPQ) (106) contains 15 items that describe the quality of chest pain and was applied at baseline and both follow-up studies. Each chest pain quality is rated on a four point scale from 0="no" to 3= "severe". The questionnaire derives a total SF-MPQ score, a sensory pain component consisting of 11 items and an affective pain component consisting of four items. The intensity of chest pain was reported on a Visual Analogue Scale from 0-100.

3.2.4. Cardiological assessments

Nine year follow-up evaluations were conducted by four cardiologists, one of whom also took part in the baseline study.

Diagnostic assessments.

In all patients, a standard bicycle ergometer test was performed according to Nordenfelt et al. (107) at baseline and at the nine year follow-up. The cardiologist conducting the test interpreted the result. The test was considered coronary artery disease positive (CAD +) if ST segment depression ≥ 1 mm occurred in any of the ECG leads during exercise. In addition, the appearance of typical chest pain, increasing ventricular ectopic beats, or absence of an increase ≥30 mm Hg in systolic blood pressure during exercise contributed to the diagnosis. When none of these signs was present, the test was considered coronary artery disease negative (CAD–). If inconclusive, the test was classified as such, and the patient was referred for further tests, such as thallium scintigraphy or coronary angiography. Referral for such investigations was determined by the cardiologist. The cardiologists were not informed of the results of the psychiatric interviews. For the purpose of final diagnostic classification, all chest pain records and results of cardiological investigations were reviewed by an independent cardiologist who

was blind to the results of the psychiatric interviews. This review did not result in any changes to the initial classification of the diagnoses.

Registration of medical diseases, medication, coronary artery disease risk factors and chest pain characteristics.

A cardiological assessment form was completed by the cardiologist for each patient at the baseline and follow-up examinations. The form recorded data on the patients' previous or prevailing medical diseases, medication and risk factors for CAD (family history of CAD before age 65 years in parents or siblings, smoking habits, diabetes, hypertension, obesity [body mass index > 26 kg/m^2] or dyslipidaemia [total cholesterol > 6.5 mmol/L and/or triglycerides > 2 mmol/L]). Chest pain was recorded with regard to presence/absence, location, pain characteristics, effect of nitroglycerine, relief by rest, chest wall tenderness and duration, and the chest pain was assigned as typical or atypical for CAD.

3.2.5. Statistical analysis

The SPSS/PC statistical package was used for all data analyses (version 10.0-14.0). For multiple comparisons a significance level of 1% was applied, otherwise the significance level was 5%.

Comparisons between groups of patients were performed using the *chi-square test* for dichotomous variables. The *independent sample Student's t test* was used for normally distributed continuous variables and the *Mann–Whitney U test* was used for continuous variables without normal distributions. The latter variables were also analyzed using Student's *t* test. As the two tests yielded nearly identical results, data are presented as the mean ± SD. All tests were two tailed. Differences between three groups were analyzed using *One-Way Analyses of Variance (One-Way ANOVA). Scheffes test* was applied for multiple comparisons. The *Paired-Sample T test* assessed change in scores of continuous variables separately for each study group.

Agreement between interviewers on psychiatric diagnoses was assessed using the *kappa coefficient.* To control for age, gender and education regarding the SF-36 scores *linear regression analyses* were conducted with SF-36 scores as the dependent variable. Baseline variables that were suspected to be associated with current PD at follow-up were entered one at a time in a *binary logistic regression analysis* with current PD at follow-up as the dependent variable. Only the variables that were statistically significantly related to PD at follow-up (P <

0.01) were considered for further analyses for model development. Variables with high intercorrelations (r >0.7) were excluded. A cut-off value of the predictors was established at a level of optimal sensitivity and specificity by inspection of the *ROC curve*.

Statistics Norway estimated the mortality rate of the entire Norwegian population during the period in which the study was conducted. The *standardized mortality ratio (SMR)* (observed deaths ÷ estimated deaths) was estimated with a 95% confidence interval (CI). The 95% CI of the SMR was calculated from the following equation: ($e^{-1,96/\sqrt{D}\,(u)} * SMR_u$, $e^{1,96/\sqrt{D}\,(u)} * SMR_u$) where D(u) is the observed number of deaths in the study population.

3.2.6 Ethical aspects.

The research protocol including the follow-up study was accepted by the Regional Ethics Committee, Oslo, in November 1994. Both at baseline and follow-up, all patients signed a consent form where they also agreed to being contacted again for future follow-up participation. On the consent form it was explicitly stated that participation in the study was voluntary, and the patients had the rights to see the data registered on them and have the data removed on any occasion. The patients received written information about the purpose of the study before all three investigations. In this information it was also emphasized that study participation was voluntary and that non-participation would have no consequence for future contact with the Cardiology outpatient clinic.

As the SCID interview contains personal questions that may be distressful for some to answer, the investigators tried to be sensitive to the patients responses. The interview of a previously traumatized patient was thus interrupted because the questions evoked unpleasant memories. Otherwise, none of the patients reported that they felt uncomfortable during the interview. In five cases the patients were referred by the investigator to treatment in a psychiatric outpatient clinic because severe psychiatric disorder was uncovered, three of which reported recent suicidal ideation. When somatic disorders requiring further medical investigation or treatment were diagnosed during the cardiological investigation, the cardiologist referred the patient to such treatment or informed the general practitioner about the necessity of further investigation in a written report.

4.0. Summary of papers.

Paper I

A 1-year follow-up study of chest-pain patients with and without panic disorder.
Gen Hosp Psychiatry 2006 Nov;28(6):516-24.

The first paper is a follow-up of 199 chest pain patients assessed at a cardiology outpatient clinic one year previously. At the baseline investigation 32 patients (16%) suffered from coronary artery disease (CAD) and 76 patients (38%) suffered from panic disorder (PD).

The aims of this study were to: (1) study the persistence of PD after one year; (2) investigate the association between PD at baseline and outcome in terms of chest pain, psychiatric morbidity, psychological distress, suicidal thoughts and health related quality of life (HRQOL); (3) study the course of pain, distress, symptom attribution and HRQOL; and (4) describe treatment and perceived treatment needs of PD patients.

The follow-up assessments included a psychiatric interview (SCID I) and self-report questionnaires (McGills Pain Questionnaire (MPQ), Symptom Checklist-90-R (SCL-90-R), Illness Attitude Scale (IAS), and The Medical Outcome Study Short Form-36 (SF-36)). After one year, one patient had died and one patient had suffered a major stroke. Of the 197 eligible patients, 153 (78%) participated in the follow-up investigation.

Among the participants were 55 patients diagnosed with PD at baseline and 43 of these (78%) still suffered from PD at follow-up. PD at baseline was associated with chest pain persistence and psychiatric morbidity (current major depression, pain disorder and simple phobia) at follow-up. The baseline PD patients had also significantly higher follow-up scores of SCL-90-R anxiety, depression and somatization, hypochondriasis (IAS), and lower scores on seven of the eight SF-36 dimensions of HRQOL compared to NoPD patients. Still, after one year only 6% of the PD patients used effective treatment and 3% reported a treatment need at follow-up.

The results suggest that only a minority of chest pain patients with PD receive anti-panic treatment one year after they are diagnosed with PD and despite continual panic attacks, chronic distress and impairment.

Paper II

Nine-Year Follow-Up of Panic Disorder in Chest Pain Patients: Clinical Course and Predictors of Outcome. Psychosomatic Medicine. Submitted.

The aims of this study were to: (1) study the persistence of panic disorder (PD) after nine years; (2) investigate the association between PD and long-term outcomes in terms of psychiatric morbidity, psychological distress, and health-related quality of life (HRQOL); (3) identify predictors of having persistent PD after nine years among baseline PD patients.

The nine-year follow-up assessments included a psychiatric interview (SCID I) and the same self-report questionnaires as included at the one-year follow-up. After nine years 14 patients were deceased and one had suffered a major stroke. Of 184 eligible patients, 150 (82%) participated in the follow-up study.

Among participants with PD at baseline (N = 55), 14 (25.5%) suffered from persistent PD at follow-up. PD at baseline was associated with a higher prevalence at follow-up of co-morbid axis I disorders (hypochondriasis and major depression), higher psychological distress, and poorer HRQOL compared with patients without PD at baseline. A mean baseline SCL-90-R somatization score above 1.4 predicted a fivefold increased risk of having persistent PD at follow-up. Patients with persistent PD had particularly poor outcomes regarding co-morbid axis I disorders, suicidal ideation (21%), psychological distress, and HRQOL. After nine years, 31% of the patients with persistent PD and 15% of patients with PD in remission received pharmacological antipanic treatment and none received cognitive therapy.

The results suggest that despite a high remission rate of PD in patients with chest pain, many PD patients still suffer from significant psychiatric morbidity and quality of life impairment after nine years. PD patients with high somatization scores require special attention because they have an increased risk of having continual panic attacks and subsequently particularly poor outcomes.

Paper III

A long-term follow-up study of chest pain patients: Effect of panic disorder on mortality, morbidity, and quality of life. Cardiology. In press.

The aims of the third paper were to (1) compare the mortality rate of chest pain patients with that of the general population; (2) examine the long-term relationship between PD at baseline and mortality, CAD, and coronary risk factors at follow-up; and (3) compare the

outcomes of chest pain patients with or without PD at baseline in terms of chest pain, anxiety, depression, and HRQOL nine years after the initial baseline examination.

One hundred and ninety-nine patients consecutively referred to a cardiological outpatient clinic because of chest pain were reassessed after nine years by a cardiological examination including a bicycle exercise test and recording of risk factors for CAD. The patients also filled in self-report questionnaires regarding chest pain, anxiety and depression (SCL-90-R) and HRQOL (SF-36). Statistics Norway compared the death rate in the sample to that of the Norwegian general population. At the initial examination 32 patients (16%) suffered from CAD and 76 patients (38%) from PD.

The death rate in the study population was not significantly different from that in the general population and no significant associations were found between PD at baseline and mortality and cardiac morbidity at follow-up. PD at baseline was associated with significantly higher follow-up scores of chest pain intensity, depression and anxiety; and lower SF-36 scores indicating HRQOL impairment (physical functioning, role physical, body pain, and general health).

The length of follow-up may have been too short to find an increased death rate in this patient sample; however, the results suggest that PD has a negative long-term effect on psychological and physical well-being of chest pain patients which emphasize the necessity of identifying PD patients and offering them adequate treatment.

Paper IV

Nonfearful panic disorder in chest pain patients. Psychosomatics 2004 Jan;45(1):69-79.

The aims of this study were to: (1) Investigate the prevalence of nonfearful panic disorder (NFPD) among chest pain patients with PD; and (2) Compare patients with NFPD to PD patients reporting fear and NoPD patients regarding demographic variables, self-reported anxiety, agoraphobia and somatization, co-morbid axis I disorders including somatoform disorder, presence of somatic disorders, alexithymia and health related quality of life in 199 chest pain patients consecutively referred to cardiological outpatient investigation.

Seventeen (22%) of the PD patients fulfilled the criteria for NFPD. Demographically no significant difference was found between the patients with NFPD and those with PD with fear. The NFPD patients differed from PD patients in lower scores on self-reported panic symptoms and lower frequency of agoraphobia. Presence of somatoform disorder, alexithymia or somatic disorder did not explain NFPD symptoms; yet, the prevalence of somatic disorders was high in

this group. Our findings confirm that NFPD is a subgroup of PD which needs to be identified as their health related quality of life impairment is not significantly different from that of PD patients reporting fear.

Paper V

Nonfearful panic disorder in chest pain patients: status after nine-year follow-up. Psychosomatics. In press.

The fifth paper is a nine year follow-up study of the patients described in paper IV. The aims of this study were to: (1) Explore the concept of NFPD by making diagnostic reassessments after nine years, and (2) Investigate the long-term outcome of NFPD patients in terms of psychiatric co-morbidity, psychological distress, chest pain, somatic diseases, health care utilization and HRQOL.

We studied 199 patients previously referred to cardiology outpatient investigation because of chest pain. At baseline a total of 76 patients suffered from PD of which 17 fulfilled criteria for NFPD. Eleven patients with baseline NFPD and 44 patients with PD with fear at baseline met to the follow-up investigation. The follow-up assessments included a cardiological and psychiatric investigation.

After nine years, no patients suffered from NFPD but seven (64%) of the patients with baseline NFPD fulfilled diagnostic criteria for either current or lifetime PD with fear. There was no significant difference between the baseline NFPD and PD patients regarding prevalence of psychiatric co-morbidity, or self-report of chest pain, health care utilization, and HRQOL at follow-up. These results strongly suggest that NFPD is a subgroup of PD which needs to be recognized as such to initiate treatment and avoid long-term impairment. Future studies should investigate the effect of recommended PD treatment on NFPD patients.

General discussion

5.1.0. Methodological issues.

5.1.1. Sample

The study is the most extensive follow-up study of chest pain patients with panic disorder to date. The sample size is larger than in the study by Beitman and colleagues (15) who followed 72 chest pain patients of whom 36 suffered from PD; and the participation rate is considerably higher than in the study by Fleet and colleagues (16) where only 54% took part in the follow-up assessments. The participation rates in the present study were 77% (153/199) at the one year assessments and 75% (150/199) at the nine year assessments regarding the total sample and 78% (153/197) and 82% (150/184) respectively regarding eligible patients (deceased and stroke patients excluded). We considered the size of the sample at follow-up large enough to determine the prevalence of persistent PD among the patients with PD at baseline and to compare the PD and NoPD patients regarding outcome measures. However, regarding prevalence of cardiac events and deaths in the PD and NoPD patients, the sample was considered too small to make statistical comparisons between the study groups (paper III). The sample size was also considered insufficient to make separate comparisons of the death rate in each of the study groups to that of the general population (paper III).

Generalizability.

The question about generalizability of the results concerns both the loss of patients from baseline to follow-up (internal validity) and to what extent the baseline sample is representative for patients with chest pain that present at the cardiology outpatient clinic. Another issue is to what degree the results may be generalized to other groups of chest pain or PD patients (external validity).

Internal validity

A methodological issue encountered in follow-up studies is whether the participating patients are representative for the initial sample studied or whether a systematic subject loss has occurred. Theoretically one might assume that patients with more somatic symptoms, more worry about their health, and more disease conviction or true medical disorders would be more

interested in participation in the follow-up investigations. Additionally, patients who work and feel well might not be willing to spend time going through a relatively time-consuming interview and exercise test. Another possibility might be that less psychologically minded patients would be less interested in discussing psychological causes of their somatic symptoms and thereby bias the follow-up sample towards those attributing chest pains to psychological causes.

To assess whether subject loss was systematic we compared the participants to the non-participants at both follow-up investigations with regard to baseline data. At the one-year follow-up the groups differed only in terms of age, but at the nine year follow-up there was no significant difference between the groups when including only eligible patients. However, when comparing the non-eligible (i.e. deceased) patients to the participants we found a significant difference with regard to the physical functioning subscale of SF-36 which we speculate was caused by a poor physical health that finally lead to death. Thus, we consider the participating patients at the nine year follow-up to be fairly representative for the baseline sample, but as the participants at the one-year follow-up was older than the non-participants the results may be skewed towards higher use of medical care and lower rate of PD (108).

The representativity of the baseline sample has been thoroughly described by Dammen in her thesis (109) where she concluded that the sample included in the study was fairly representative of chest pain patients referred to the cardiological outpatient clinics at that time.

External validity

The present study was conducted in patients consecutively referred to investigation of non-acute chest pain and one should be cautious to generalize the results to other chest pain or PD samples. Although the baseline sample was considered representative of chest pain patients referred to the cardiological outpatient investigation nine years ago, we do not know if it is representative for chest pain patients referred to the outpatient clinic today. At baseline only 16% of the sample suffered from CAD, unfortunately, we are not aware of any recent studies addressing the prevalence of CAD among chest pain patients referred to cardiology outpatient clinics to make comparisons.

Moreover, in the present sample the majority of patients (123/199; 62 %) described chest pain characterized as atypical (39), the mean duration of chest pain was relatively long (> 5 years in NCCP patients and 1,5 year in CAD patients) (39), only 10 patients were referred to coronary angiography and 57 patients were referred to thallium scintigraphy. Thus, the outcome of these patients with regard to future cardiac events and mortality may be lower than

in patients with more typical angina (20) or more acute chest pain onset (13).Whereas it may be higher than among those who have been diagnosed with NCCP based on negative angiography (15). In addition, traditional risk factors for CAD were identified at the baseline investigation in all patients and may have been treated, thus possibly decreasing the risk for future CAD development.

One must also be cautious with generalizing the results to PD patients in psychiatric settings. Unfortunately we did not record the age of onset of PD at the baseline investigation and therefore have no information regarding the duration of PD in this sample. As discussed in section 5.2.2. we might suspect that the majority of baseline PD patients were in an early phase of the disease and therefore had lower rates of co-morbid psychiatric disorders than is usually seen in PD patients in psychiatric clinics. A higher rate of co-morbid depression might have contributed to the development of CAD in more patients as co-morbid depression increased the risk for subsequent cardiac events in a cohort study of PD (85). The mean age of the patients was higher than reported in most studies of PD in psychiatric settings. This may also have influenced outcome as studies of late-onset PD have reported a less severe disorder in terms of psychological distress and psychiatric co-morbidity in older as opposed to younger PD patients (29). One study reported that panic symptoms tended to wear off while somatization increased in older PD patients (108).

5.2.1. Assessments

5.1.2.1. Psychiatric assessments.

Diagnostic assessments.

Psychiatric diagnoses were recorded by using the SCID interview for Axis I diagnoses at baseline and at both follow-up studies. This is the first study to make diagnostic reassessments at follow-up in chest pain patients with PD which make comparisons with previous studies of PD in cardiac settings difficult. Fleet and colleagues (16) used a detection model to estimate the prevalence of PD after two years and reported that 96% of the PD patients still suffered from PD at follow-up. But we cannot exclude the possibility that this might be an overestimation due to his methodology. The SCID I interview is known to yield highly reliable diagnosis of Axis I disorders (110) and it is often considered to be the gold standard of diagnostic assessments in clinical research. In the present study, two different persons (TD/CBB) performed the interviews and made the diagnostic evaluations. This implies

a possibility for different judgments by the raters. Thus, differences in prevalence of psychiatric disorders from baseline to the nine-year follow-up (paper II) might have been caused solely by different judgment. To estimate the ability of two different observers to yield the same result, an inter-rater reliability measure was applied (see section 3.2.1). Since TD made the secondary diagnostic ratings at the nine year follow-up and the results of this test was considered to be good to excellent, we can be fairly confident that the diagnostic assessments are reliable.

Moreover, at both follow-up investigations the interviewers were blind to previous somatic and psychiatric diagnoses to avoid any skewness towards a higher prevalence of diagnoses already given. Still, it is possible that the interviewer who performed the first two diagnostic assessments may have recalled some of the patients and thus have overestimated the rate of persistent PD at the one year follow-up. At the nine year follow-up the person performing the interviews was unfamiliar with the participants and was unaware of previous diagnoses which may have lead to an underestimation of persistent PD because she could not aid the patients in recalling previous panic episodes. This make this study quite different from studies conducted in psychiatric settings in which all study participants have well-known PD and the questioning aims at differentiating between those in remission and those with persistent symptoms.

Although the SCID interview is a reliable tool in psychiatric research its application in clinical settings and its correlation with simpler diagnostic assessment methods is questionable (110). An advantage with the present study was that the diagnostic assessments were conducted as part of a routine cardiological evaluation of chest pain and not applied in a more standardized research setting. On the other hand, the interviewers had generated a considerable amount of experience in performing SCID interviews and the ratings might therefore differ from clinicians with less experience (110).

Using a panic disorder diagnosis in patients with high rates of medical diseases is somewhat complicated as the diagnostic criteria for PD states that the symptoms should not be due to an underlying medical condition or the physiological effect of a substance (medication, drug abuse). In paper IV we estimated the prevalence of PD excluding all patients with any medical condition and still found a PD prevalence of 18 %.

Self-report questionnaires.

For most purposes we used questionnaires that are well-validated and widely used clinically and in research. They were either authorized translations (SCL-90-R, SF-36, ACQ,

MIA) or were translated and back-translated by a language consultant at the baseline investigation (SF-MPQ, PDQ, TAS-20, IAS).

Nevertheless, there are some possible pitfalls that need to be considered. First, one should consider problems with the reliability of the questionnaires in the sample studied. One problem that appears is the high frequency of medical diseases in the present sample (62% had one ore more medical disease) and the possibility that the symptoms of these diseases are recorded as somatization on the subscale of SCL-90-R. To test out this possibility the patients without any medical condition were compared to those with one or more conditions regarding SCL-90-R somatization. We found that the patients without any medical disorder had a significantly lower score both at baseline and nine year follow-up (data not shown in papers). The number of medical disorders was also significantly correlated with the SCL-90-R somatization subscale but not with any of the other subscales of SCL-90-R. Thus, we cannot with certainty claim that the SCL-90-R score signify "true" somatization i.e. physical symptoms in the absence of a medical explanation, however there is also some uncertainty regarding the accuracy of the self-reported medical disorders as discussed below in section 5.1.2.2.

Second, there may be a problem with retrospective data collection. At the one year follow-up patients were asked to report number and types of hospitalizations and appointments with their general practitioner, medical specialists etc. during the last year. Their recollection may not have been correct and their reports were not verified by objective measures. However, we do expect that problems with recollection would be similar in the groups compared.

Third, the possible presence of confounding variables needs to be considered (i.e. when the association between the two variables of interest is influenced by the impact of a third variable). Regarding the SF-36, previous research has reported an association between age, gender, income and the SF-36 subscale scores (101). Hence these variables were controlled for when making statistical comparisons. One might also suspect that major depression would influence the association between PD and suicidal ideation (111) and between PD and HRQOL. This would especially influence the relationship between persistent PD at follow-up and the above mentioned outcome variables as the prevalence of major depression among the patients with persistent PD was 50% (Paper II). However, controlling for major depression did not yield significantly different results.

5.1.2.2. Cardiological assessment

A standard bicycle exercise ECG was performed twice; at baseline to detect whether CAD was the cause of chest pain and at the nine year follow-up to estimate the proportion of patients who had developed CAD. Although the classification of CAD and non-CAD was considered to be reliable at baseline, there was a concern that CAD might have been underestimated (14) as the result of the exercise test was verified by angiography in only ten patients and by thallium scintigraphy in 57 patients. According to a joint report of the American College of Cardiology/ American Heart Association: Guideline for Exercise Testing the exercise test is most useful as a diagnostic test in patients with intermediate pre-test (25-75%) probability for CAD (including risk factors such as age, gender and chest pain characteristics) (112). In chest pain patients the estimated sensitivity and specificity of the exercise ECG are 50% and 90% respectively (112). Thus, the test would be negative in 90 % of patients without disease and positive in only 50% of patients with disease, thus the possibility for underestimation of CAD (i.e. false negative results) is obvious. Still, when reaching a final diagnosis of CAD or non-CAD general guidelines for routine handling of chest pain patients were followed. This includes risk assessments with regard to age, sex and chest pain characteristics in addition to the results of the exercise ECG (112). The validity of this procedure was probably confirmed by the results of paper III showing that only 7.8% (13/167) of patients without CAD at baseline had experienced a cardiac event (including cardiac deaths) by the time of the nine year follow-up.

The accuracy of the exercise ECG at the nine year follow-up investigation is more questionable because the patient sample at that time was more heterogeneous i.e. 43% reported no chest pain and about 25% had known CAD. To use the exercise ECG as a diagnostic test in asymptomatic patients is not recommended (112) as it increases the risk for false positive results. However, the present study had the advantage that all patients had performed at least one previous test and the results of the two tests could be compared. Regarding the patients with known CAD the result of the exercise test had no effect on the diagnostic decisions, but as the researchers were blind to previous diagnosis, all patients had to go through the same procedure.

The cardiologist also recorded the presence of risk factors for CAD and the presence of other diseases than CAD such as asthma, migraine, diabetes, gastrointestinal disease, musculoskeletal disorders and hypo- and hyperthyroidism. However, the presence or absence of a disorder was based on the patients self-report and information from the medical record at

the Ullevål University hospital and not by objective investigations which were considered beyond the scope of this study. As thoroughly discussed in paper V, this implies that some of the disorders may represent what the patients believed they suffered from and not a true physical condition. This also affects the discussion of the reliability of the somatization score above and denotes that the distinction between medically explained and unexplained symptoms is somewhat vague in the present study.

With regard to risk factors for CAD, the same risk factors were recorded at the nine year follow-up as was done at baseline to make comparisons. These risk factors may not have been the most appropriate. In a recent worldwide multicenter study of risk factors for CAD the Apo lipoprotein concentrations and ApoB/ApoA1 ratio was used because they are not affected by the fasting status of the individuals (113). In the same study the waist/hip ratio proved to affect the risk for CAD more strongly than the BMI. Both the waist/hip ratio, ApoB/ApoA1 ratio and number of cigarettes smoked showed a linear relationship with risk for CAD and should therefore rather be used as continuous variables than as dichotomous variables as done in the present study.

5.2.0. Results and clinical implications.

5.2.1. Prevalence of panic disorder at follow-up.

At the one-year follow-up 78% of the patients with PD at baseline, still met the criteria for current PD. At the nine year follow-up, this rate had dropped to 25.5%. These rates of PD persistence are similar to rates reported in a 4-10 month follow-up in primary care (114) and 6-15 years follow-up in psychiatric settings (46-48). These results have several implications.

First, when diagnosing PD in chest pain patients using a diagnostic tool such as the SCID I, the physician doing this can be confident that this diagnosis is as valid as a PD diagnosis given in a psychiatric setting. The possible problem by applying PD diagnoses in patients with medical disorders is discussed in section 5.1.2.1. One might also suspect that the uncertainty of experiencing chest pain could have initiated panic attacks in some patients and that a cardiological evaluation would relieve the anxiety. However, only 22% of the PD patients had remitted during the first year after the evaluation. This is in line with Lantinga et al. who reported that high levels of neuroticism was not only associated with anticipatory stress before cardiac catheterization, but persisted one year after the procedure was carried out (25).

Second, the rate of remission of PD after one and nine years seems to be independent of pharmacological PD treatment. Only 10 % of the patients in the present study had received antidepressants or high-potency benzodiazepines (paper I and II). Two follow-up studies of PD in psychiatric clinics also reported that remission of PD was not related to initial trial treatment (44) or intake of antidepressants or benzodiazepines the week before follow-up (43). In a recent Cochrane review (70) either a combination of psychotherapy and antidepressants or psychotherapy alone was recommended as first choice of treatment for PD which none of the patients in the present study received. Another issue is whether such treatment is available and acceptable to these patients (see section 5.2.4).

Third, based on clinical impression and the results of this study, it may seem as if the course of PD in chest pain patients is not uniform but rather form three subgroups of courses. As described in paper II, after nine years a little more than one third (38%) did not report current or past PD symptoms and it is reasonable to believe that these patients had remitted and were well. About one quarter (25.5%) fulfilled criteria for current PD and reported a particularly poor outcome regarding psychological distress, suicidal ideation and HRQOL as discussed later. Finally, about one third (36%) reported lifetime PD, but did not fulfill criteria for current disorder. Katschnig and colleagues suggested a similar differentiation of PD courses (see section 1.2.) (44;45). In their study about one third of the patients remitted and stayed well, 45 % had a chronic persistent course (of whom about half were severely disabled) and one quarter had a fluctuating course. Thus, it is evident that some PD patients do better and some do worse and a future task is to learn how to differentiate between patients with different courses at an early stage of the disease.

5.2.2. Outcome of panic disorder at follow-up.

The outcome of the baseline PD patients were significantly worse than the NoPD patients at both the one year and nine year follow-ups with regard to chest pain persistence, psychological distress, hypochondriacal concerns and HRQOL. Regarding the majority of outcome measures applied, the scores of the PD patients had not changed significantly from baseline to any of the follow-up investigations. This means that the levels of self-reported distress and functioning are quite stable phenomena in these patients. This confirms the results by Katschnig and colleagues (63) who reported that the only predictor of disability after four years was the baseline disability score; and Noyes and colleagues (51) who found that symptoms at baseline was highly predictive of symptom severity after three years.

With regard to co-morbid psychiatric disorders, the most striking finding was the increasing prevalence of major depression from 9% at baseline to 18% after one year and 29% after nine years. Although depression co-occurred with PD less frequently at baseline than is usually reported in studies of PD in psychiatric settings, the prevalence of co-morbid depression after nine years was similar to that reported in a review of follow-up studies of PD (55). Three possible explanations to the panic-depression co-morbidity have been suggested: depression as a causal risk factor for panic, panic as a causal risk factor for depression or panic and depression both as consequences of another disorder (115). The results of the present study may indicate that depression developed as a consequence of having had PD for several years.

Moreover, the patients with persistent PD after nine years had a particularly poor outcome. This is in line with Katschnig and colleagues (63) who identified a subgroup of PD patients who were severely disabled at follow-up and asked: Who are these patients and could they be identified at an early stage? They did however not provide an answer. We found that the patients who still suffered from PD after nine years had very low HRQOL scores, in fact their scores were not much different from patients with terminal cancer (116). In addition they reported a high rate of suicidal ideation at follow-up as three of the 14 patients reported having had suicidal thoughts last week. High rate of suicidal ideation has previously been reported in PD patients with acute chest pain seen in an emergency department (117). The patients with persistent PD in the present study had several risk factors for suicidal ideation. PD may in itself be an independent risk factor and patients with PD and co-morbid depression are at especially high risk (57;58). They had high somatization scores and somatization has been independently associated with suicidal ideation (118). Furthermore, 100% of the patients had persistent chest pain and a previous study reported that chronic pain was associated with a three-fold increased risk for suicidal ideation (119). We don't know if suicidal ideation is associated with suicide attempts in this sample, nevertheless, suicidal ideation is a manifestation of severe distress and personal suffering.

Based on the assumption that PD patients often initially present with one or more somatic symptoms (120) and the relatively low prevalence of co-morbid psychiatric disorders at baseline, we speculate that the patients included in the present study had a shorter duration of PD than that of most patients in psychiatric settings. This may seem contradictory since the mean age of the PD patients was higher than what is reported of PD in psychiatric settings. We hypothesize that a proportion of the patients in the present study have "late-onset" PD (see section 1.2.0.). The mean and median age of the PD patients at baseline was 48 years (range 20-65 years), but unfortunately the age of onset of PD symptoms was not recorded. "Late-

onset" PD is identified in patients in primary care (26), psychiatry clinics (121), and among chest pain patients in cardiology clinics (28) and is characterized by milder symptoms and lower prevalence of co-morbid axis I disorders (26;29;121) as compared to PD patients with earlier onset.

The PD patients included in the present study nine years ago may have had a less symptomatic and debilitating disease than most PD patients in psychiatric settings have. Similar results were reported by Fleet and colleagues who compared PD patients recognized in an emergency department to PD patients in a psychiatric clinic (122). However, the results of the follow-up study we have conducted, suggest that during the course of the disease, they develop major depression at they same rate as PD patients seen in psychiatric care and a subgroup of patients may have a severe chronic course. Co-morbid panic and depression are markers of a more persistent and severe disease (123). Therefore, recognition PD in cardiac settings may be an opportunity to provide early treatment and prevent further chronification and disability.

5.2.3 Predictors of persistent PD.

In order to identify PD patients with a particularly unfavorable long-term prognosis, we established predictors of having persistent PD after nine years by applying a logistic regression analysis. The only variable that was independently related to PD was the baseline SCL-90-R somatization subscale score (paper II). A high somatization score and high disease conviction were also characteristics of patients who did not remit from hypochondriasis in a follow-up study of hypochondriacal patients (124). How can this result be interpreted? The SCL-90-R subscale consists of 12 physical symptoms and a high score is obtained when the patients report many symptoms or high distress in relation to symptoms. One need to consider whether both high somatization and PD persistence are caused by another condition characterized by a poor prognosis or whether there is a causal relationship between a high somatization score and PD persistence.

First, the presence of a personality disorder may be a possible confounder as it often co-exists with somatization disorder (72%) (125) and may negatively affect the outcome of PD (67). At baseline, significantly more of the PD than NoPD patients suffered from avoidant and borderline personality disorders (23.7% vs. 7.7% and 12.5% vs. 2.5 %) (126) but we did not find an association between presence of a personality disorder at baseline and PD persistence after nine years (paper II). This may be explained by low statistical power because of low

prevalence of personality disorders and should be replicated in larger samples of chest pain patients. Second, alexithymia may be another possible, although less likely, confounder of PD and somatization. The term alexithymia means “no words for feelings” and was introduced by Sifneos to describe this characteristic in psychosomatic patients (127). Alexithymic PD patients would less likely communicate their distress to their physicians and therefore not receive PD treatment. However, the association between alexithymia and somatization is questionable. In a meta-analytic review of studies concerned with the association of alexithymia and somatization (128), only a small to moderate relationship was reported and most studies included had not controlled for anxiety and mood disorders. Another study reported that the association between alexithymia and somatization was limited to patients with psychiatric disorders who denied a relationship between somatic symptoms and emotional problems (129). In the present sample, PD patients did not differ from NoPD patients in terms of alexithymia (paper IV) and they did not deny a psychological causation but rather considered it the most likely cause of their chest pain at the one-year follow-up (paper I).

In patients with a high number of physical complaints there is a risk that psychological problems are overlooked by the patients and their physicians because they focus on the physical symptoms (121). Subsequently the patients with persistent PD may be those who also were medically ill and in whom the illness produced worrying physical symptoms (i.e. chest pain, palpitations, breathlessness etc.) which initiated panic attacks. The symptoms of these illnesses might have been wrongly scored as somatization which is discussed in section 5.1.2.1. However, there was no significant difference in mean number of medical disorders at baseline between the patients with persistent PD compared to those with PD in remission (1.6 disorders in both groups) at follow-up.. Thus, the high somatization score of the patients with persistent PD was presumably caused by medically unexplained symptoms. The SCL-90-R somatization subscale consists of 12 somatic symptoms of which some are overlapping with symptoms of panic attacks (i.e. breathlessness, chest pain, dizziness) and some are not (i.e. low back pain, headache, weakness of the limbs). High number of medically unexplained symptoms has in a previous study been associated with poor outcomes in terms of psychiatric co-morbidity, disability and health care utilization in primary care patients (130).

The somatization score of SCL-90-R may help clinicians to identify the PD patients with the poorest outcome. Several authors have made models for detections of PD in chest pain patients (131;132) although none are established as guidelines. The results presented in paper II extends previous detection models by intending to discriminate between PD patients with poor as opposed to more favorable outcome in terms of PD persistence/remittance. We found

that a SCL-90 somatization subscale score above 1.4 gave a fivefold increased risk of having persistent PD at follow-up among the baseline PD patients. This result needs to be replicated in other PD samples.

None of the co-morbid disorders (major depression, hypochondriasis and personality disorder) associated with persistent PD in studies from psychiatric settings predicted persistent PD in the present sample (paper II). The most obvious explanation is the low rate of these disorders at baseline (major depression 12%, hypochondriasis 7%, PDQ personality disorders 4-25%) (14). However, we may also speculate that the PD patients in the present sample were in an early phase of the disorder and that different factors determine whether the course of the disorder will become chronic, or an already chronic disorder will remit.

5.2.4. Treatment and perceived treatment need.

At the baseline investigation Dammen et al. reported that only three of the 76 PD patients were previously informed that they suffered from PD, nine (12%) of the patients received treatment with an anti-depressant or benzodiazepine and 32 (45%) of the patients reported a treatment need (14). Undertreatment of PD in chest pain patients have previously been related to non-recognition by physicians (13), but in the present study all PD patients were identified and still only a minority received effective PD treatment at follow-up (Paper I and II). The present study does not provide answers to why the majority were untreated. One previous study have reported that undertreatment of PD in primary care was more related to patient characteristics than to physicians specialty and training (49). A major limitation of the nine-year follow-up is that we have very little information about the treatment received between the investigations as we only asked for treatment last year. Thus, we may assume that the total amount of treatment received is somewhat higher than the reported current treatment, but that treatment has been discontinued during the follow-up period.

This raises some important questions regarding willingness of the patients to receive and adhere to psychological treatment. In a controlled trial of cognitive therapy for chest pain patients a significant number of patients refused to participate or dropped out because they considered the treatment too “psychological” (133), partly because assessments were conducted in the Department of Psychological Medicine. A population based study reported that 73% of patients with anxiety symptoms did not seek health care because of attitudinal reasons such as: “I preferred to manage myself”, “I didn’t think anything could help” and “I was afraid to ask for help” (134). Moreover, about 50% of PD patients discontinue

antidepressant treatment (135). Non-adherence has often been attributed to high sensitivity for side effects which is common in PD patients (136) and in patients who tend to somatize (137). Yet, in a study of 326 PD patients side-effects were the cause of treatment discontinuation in only 10% of non-adherent patients, whereas 37% considered further psychiatric treatment as unnecessary because of remission and an additional 18% reported ineffectiveness as the reason for discontinuation (135). PD patients' beliefs about psychotropic medication and psychosocial treatment are of crucial importance in terms of adherence to treatment (138), thus, there is a need to elucidate attitudes towards such treatment in chest pain patients with PD. A brief measure has recently been developed to identify beliefs about psychotropic medication and psychotherapy which should be applied in these patients (138).

Another crucial issue is to what extent treatment is available for chest pain patients with PD. General practitioners are presumably the physicians with a broader view of the patients' health and should be able to identify PD in chest pain patients and implement treatment. Dammen and colleagues developed a screening questionnaire to aid the recognition of PD in chest pain patients (131), but careful understanding of PD symptoms and knowledge regarding PD treatment are essential. When general practitioners meet patients with chest pain, PD should be one of the diagnoses under consideration and especially so if there is no organic cause to the pain. It is also important to communicate this to the patients early in the investigation process rather than label the symptoms "only anxiety" when no "real" disease is found. Roy-Byrne and colleagues have suggested a detailed practical guideline for the management of PD in primary care (50).

Moreover, Mayou and colleagues have proposed a stepped-care approach to the management of non-cardiac chest pain were the staff of the cardiological department plays a central role in close collaboration with liaison psychologists or psychiatrists (139). This approach includes:1) reassurance of the negative results of the cardiological investigations; 2) a six week follow-up to repeat reassurance and to address persisting chest pain and distress, give alternative explanations to chest pain and treat those with pain suspicious of acid reflux by a trial of proton pump inhibitors (140); 3) a three to six months follow-up to confirm improvement for those with only mild symptoms at the first follow-up; 4) regular follow-up appointments for those with persistent chest pain who are highly distressed or experience severe disability. For some patients a psychological intervention may be indicated. Mayou recommends that the cardiologist refer the patients to such treatment as part of a standard procedure to make it more acceptable. We believe an approach similar to that proposed by Mayou would be the best way to recognize PD and provide treatment at an appropriate level.

The results of the present study suggest that the course of PD is not uniform (section 5.2.1.) accordingly; the need for treatment will probably be differentiated. Some may need reassurance only, some need more regular follow-up perhaps including a period with anti-panic medication or a cognitive behavioral intervention; and a third group will need more extensive psychiatric treatment. Future studies should implement treatment of PD (described in section 1.2.6) in chest pain patients to achieve knowledge with regard to acceptability and effect of such treatment in these patients.

5.2.5. Effect of panic disorder on chest pain persistence, cardiac morbidity and mortality.

At the one year follow-up 78% of the patients reported persistent chest pain, significantly more of the PD compared to the NoPD patients (90% vs. 72%). At the nine year follow-up the rate of persistent chest pain was 57% for the total sample, but opposed to previous studies reporting an association between PD and chest pain persistence (15;16), the PD and NoPD patients did not differ significantly (64% vs. 54%). Still, the rate of chest pain persistence among the PD patients was similar to the rate reported in previous studies, but the rate was high among NoPD patients as well. This may be explained by diseases such as dyspepsia, asthma and muscelo-skeletal disorders which occurred frequently in both PD and NoPD patients (see table 5, paper V). There was no significant difference in rate of persistent chest pain between patients with and without CAD (76% vs.79% after one year and 51%vs. 62% after nine years). The results of this study suggest that among patients referred to a cardiology outpatient clinic because of chest pain, more than half still have chest pain after nine years.

An important aim of the study was to explore the association between PD and future coronary events as none of the previous follow-up studies of PD in chest pain patients have included a second cardiac evaluation. One concern was that cardiac disease was overlooked at the baseline investigation as discussed in section 5.1.2. Another concern was that population based studies have reported an association between panic-like anxiety and risk of sudden cardiac death and an association between PD and non-fatal coronary events (see section 1.2.7.). The present study revealed no relationship between PD and subsequent fatal or non-fatal cardiac events.

One theory regarding the link between PD and CAD stresses that PD patients have a high prevalence of traditional risk factors for CAD (82). Risk factors for CAD was identified in a large case-control study of patients with myocardial infarction reporting that nine risk factors

(abnormal lipids, smoking, hypertension, diabetes, abdominal obesity, psychosocial factors, lack of moderate alcohol consumption and lack of regular exercise and consumption of fruits and vegetables) together accounted for more than 90 % of the risk in both sexes, at all ages and in all regions of the world (113). At baseline, the PD patients of the present sample reported significantly more often a positive family history of CAD and they were more often smokers than NoPD patients (14). At the nine-year follow-up there was no significant difference between PD and NoPD patients with regard to traditional risk factors (paper III).
Previous studies of traditional risk factors for CAD in PD patients have also given inconsistent results (11). Furthermore, high self-reported generalized anxiety have in fact been associated with better control of risk factors and more frequent general practitioner visits and subsequently better outcome in terms of cardiac mortality of patients referred for exercise testing (141).

The lack of risk factor elevation among the PD patients may partly explain why we did not find an association between PD and non-fatal CAD or mortality, but is probably not the only explanation. Epidemiological studies investigating the relationship between PD and CAD have controlled for differences in traditional risk factors and have still found a significant association. Another hypothesis attributes autonomic dysfunction in PD patients, mediated by reduced vagal tone or increased circulating catecholamines, as a cause of decreased heart rate variability (HRV) and increased risk of ventricular arrhythmias and sudden cardiac death (142;143). Investigations of HRV in PD patients have been conducted in small patient samples and the results have so far been inconclusive (83;144). Moreover, panic attacks have produced coronary vasoconstriction resulting in ischemia in PD patients with CAD (145) but the effect of panic attacks on normal vessels are largely unexplored. Chronic psychological distress may also influence blood coagulation and fibrinolysis, especially in patients with known cardiovascular disease (146). Thus, there are several theories regarding the possible association between PD and CAD, but the association is evidently not strong enough to produce a significant relationship in the present sample. As discussed in paper III this may be explained by a small number of deaths and new cardiac events in this sample and a too short follow-up time, hence, future studies should be conducted over a more extensive follow-up period.

5.2.5. Prevalence and outcome of nonfearful panic disorder among chest pain patients.

The results from paper IV and V expand the knowledge of the predictive and construct validity of NFPD and strongly indicate that NFPD is a panic disorder subtype. First, 22% of

PD patients (17 of 76 patients) suffered from NFPD at baseline which is in line with previous studies of NFPD in other types of chest pain samples (86-88). Furthermore, after nine years, the majority (66%) of patients with NFPD at baseline fulfilled the diagnostic criteria for either current or lifetime PD with fear (the remaining patients did not recall having had either PD or NFPD). Second, we did not find that somatoform disorder or unrecognized medical disorder would better explain the NFPD symptoms at baseline and this was confirmed at follow-up. Third, there appeared to be no significant differences between NFPD and PD with fear in demographic characteristics and outcome in terms of health related quality of life at baseline or after nine years.

However, there were also differences between PD and NFPD patients that need to be mentioned. At baseline the NFPD patients appeared to be less symptomatic with regard to co-morbid agoraphobia and self-reported anxiety, depression and panic-agoraphobia measures and this difference persisted after nine years. This result is in line with cross-sectional studies of NFPD (86-88), but it also expands previous knowledge by adding a longitudinal perspective. Additionally, the baseline NFPD patients tended not to develop the psychiatric co-morbidity (i.e. depression) during the course of the disease that characterized the total PD sample (see section 5.2.2.). In this regard the NFPD patients may have less in common with PD patients seen in psychiatric care, but perhaps be more similar to patients with somatoform disorders (i.e.36 % suffered from any co-morbid somatoform disorder at follow-up).

The concept of NFPD may be understood in the light of the psychobiological similarities between PD and somatoform disorders. Misinterpretation of bodily signals is essential in both disorders. There is evidence that patients with somatoform disorders experience persistent physiological activation which increase the risk of misinterpretation of bodily signals (147). Misinterpretation of symptoms caused by physiological arousal is also part of theories explaining panic attacks as it leads to a vicious circle of increasing autonomic activation (148;149). Moreover, the hypothalamic-pituitary axis as well as the seretonergic system may be involved in both somatoform and panic disorders (150). Future research should explore psychobiological markers of somatoform disorders and their overlap with PD with and without fear.

Nevertheless, the main body of research has concluded that NFPD is a subtype of PD and by establishing NFPD as such its identification might improve, thus preventing that a substantial proportion of PD patients is neglected. Kushner and Beitman (89) suggested that NFPD should be mentioned under the heading of PD in the DSM IV (which it eventually wasn't). This would also enable physicians to initiate treatment. Currently, research regarding

the effect of conventional PD treatment on patients with NFPD is inadequate, but one previous study has reported effect of antidepressants (92). Cognitive therapy alone or in combination with antidepressants is according to a recent meta-analysis the first choice of PD treatment (70). Although the cognitive distortions in NFPD patients seem to be less fear related than in PD patients experiencing more anxiety; i.e. they may attribute the bodily symptoms as signs of disease but not think it implies an immediate threat such as death, we hypothesize that this treatment approach would be suitable in NFPD patients as well.

General conclusions

- The rate of PD remission was similar to that reported in psychiatric PD studies, i.e. about 3/4 of baseline PD patients still suffered from PD after one year and 1/4 after nine years.
- The results suggest that the course of PD is not uniform, about 1/3 remits and stays well, about 1/4 has persistent panic attacks and serious disability and the rest experience some residual symptoms.
- The total psychiatric morbidity of the baseline PD patients was significant at follow-up (67 % had at least one other psychiatric disorder after nine years). The rate of co-morbid major depression had increased from 9% at baseline to 18% after one year and 29% after nine years.
- PD at baseline was associated with higher psychological distress and hypochondriacal concerns and poorer HRQOL at follow-up after one and nine years compared to NoPD patients.
- The patients with persistent PD after nine years had a particularly poor outcome regarding psychological distress and HRQOL and 22% reported suicidal ideation last week.
- Among baseline PD patients a high SCL-90 somatization score was a significant predictor of still having PD after nine years.
- Only a minority of baseline PD patients received pharmacological PD treatment at follow-up (6% after one year and 18% after nine years) and none received cognitive therapy.
- Patients consecutively referred to a cardiology outpatient clinic because of chest pain have an excellent long-term prognosis in terms of mortality (7%) and few patients without CAD at baseline developed CAD during the nine year follow-up (8%).
- The chest pain was chronic for many patients as 78% still experienced chest pain at the one year and 57% at the nine year follow-up. PD at baseline predicted chest pain persistence after one year and more intense chest pain after nine years.
- PD at baseline was not associated with mortality or non-fatal cardiac events at the nine year follow-up.

- Twenty-two percent of the PD patients suffered from panic attacks without fear (NFPD) at baseline. After nine years none of the NFPD patients fulfilled criteria for NFPD, but 2/3 reported current or lifetime PD with fear.
- NFPD should be recognized as a subtype of PD to avoid that a substantial proportion of PD patients are neglected.
- NFPD patients are characterized by lower psychiatric co-morbidity and lower self-reported anxiety than PD patients reporting fear and high co-morbidity with somatoform disorders.

Suggestions for future research

This is the first long-term follow-up study of chest pain patients which emphasize the importance of panic disorder. The generalizability of the results should therefore be tested in other chest pain populations i.e. among patients with acute chest pain, patients with negative coronary angiography or patients with chronic chest pain seen in primary care.

The results suggest that there are subgroups of courses of PD, a finding that should be confirmed in future studies. A high SCL-90 somatization score predicted a five-fold increased risk of having persistent PD after nine years and subsequently a particularly poor outcome of PD in the present study. This result needs replication in other chest pain populations. By being able to differentiate between PD patients with different outcomes based on characteristics of the patients early in the investigation process, one would enable physicians to focus on the patients who need the most comprehensive management.

To further explore the mortality of chest pain patients and the association between PD and cardiac morbidity and mortality, one should investigate the mortality rate after a longer follow-up time (more than 15 years).

The high prevalence of somatoform disorders and high self-reported somatization among the PD patients both at baseline and follow-up should be explored in future studies of chest pain patients. Especially with regard to patients with NFPD there seem to be a high co-morbidity with somatoform disorders. Accordingly, future studies should intend to use methods which reliably differentiate between medically explained and unexplained symptoms. There is also a scarcity of research regarding the psychobiological markers of somatoform disorders and their possible overlap with PD which should be elucidated in future research.

As effective treatment for PD exists one may assume that chest pain patients with PD would benefit from recommended treatment. However, no previous study has implemented such treatment in chest pain samples. There is therefore a need for future studies that explore the effect and acceptability of recommended PD treatment among chest pain patients with PD and NFPD. This should include assessments of beliefs about psychotropic medication and psychotherapy. There is also a need for studies that replicate the stepped care approach for management of chest pain patients proposed by Mayou and colleagues.

Tables

Table 1. DSM-IV[a] criteria for panic disorder

A. Both (1) and (2)
    1. Recurrent unexpected attacks of intense discomfort or fear.
    2. At least one of the attacks has been followed by one or more of the following:
        a) sustained fear of new attacks,
        b) fear of the consequences of attacks,
        c) significant change in behavior related to the attacks and lasting for one month or more.

B. The attacks consisted of at least four of the following: palpitations, sweating, trembling, shortness of breath, choking, chest pain, nausea, dizziness, derealization or depersonalization, paresthesias, chills, flushes, fear of dying or fear of going insane or losing control.

C. The panic attacks are not due to the direct physiological effect of a substance (e.g., drug abuse, medication) or a general medical condition (e.g., hyperthyroidism).

D. The panic attacks are not better accounted for by another mental disorder.

[a] *Diagnostic and Statistical Manual of Mental Disorders, 4th ed.*

Table 2. DSM-IV[a] Criteria for nonfearful panic disorder.

A. Both (1) and (2)
    1. Recurrent unexpected attacks of intense discomfort without fear.
    2. At least one of the attacks has been followed by a significant change in behavior related to the attack lasting for one month or more.

B. The attacks consisted of at least four of the following: palpitations, sweating, trembling, shortness of breath, choking, chest pain, nausea, dizziness, derealization or depersonalization, paresthesias, chills or flushes (no fear of dying, of going crazy or losing control).

C. The panic attacks are not due to the direct physiological effect of a substance (e.g., drug abuse, medication) or a general medical condition (e.g., hyperthyroidism).

D. The panic attacks are not better accounted for by another mental disorder.

[a] *Diagnostic and Statistical Manual of Mental Disorders, 4th ed.*

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