Musculoskeletal Chest Pain
Diagnosis and manual treatment in patients with acute chest pain
admitted to an emergency cardiology department

PhD Thesis

Mette Jensen Stochkendahl

Institute of Chiropractic and Clinical Biomechanics, University of Southern Denmark
Nordic Institute of Chiropractic and Clinical Biomechanics
Department of Nuclear Medicine, Odense University Hospital
Department of Cardiology, Odense University Hospital

Faculty of Health Sciences
University of Southern Denmark
2009
PREFACE

Supervisors
Jan Hartvigsen (principal supervisor)
Nordic Institute of Chiropractic and Clinical Biomechanics,
Part of Clinical Locomotion Science
Odense, Denmark
&
Institute of Sports Science and Clinical Biomechanics,
Part of Clinical Locomotion Science
University of Southern Denmark
Odense, Denmark

Henrik Wulff Christensen (project supervisor)
Nordic Institute of Chiropractic and Clinical Biomechanics,
Part of Clinical Locomotion Science
Odense, Denmark

Werner Vach
Clinical Epidemiology
Institute of Medical Biometry and Medical Informatics
University Medical Centre Freiburg
Germany

Poul Flemming Høilund-Carlsen
Department of Nuclear Medicine
Odense University Hospital
Odense, Denmark

Torben Haghfelt
Department of Cardiology
Odense University Hospital
Odense, Denmark
List of study publications

This thesis is based on the following papers:

Paper I

Paper II
Stochkendahl MJ, Christensen HW, Hartvigsen J, Høilund-Carlsen PF, Haghfelt T. Non-cardiac chest pain in patients admitted to an emergency cardiology department (Submitted).

Paper III
Stochkendahl MJ, Vach W, Høilund-Carlsen PF, Haghfelt T, Hartvigsen J, Christensen HW. Cervicothoracic angina identified by case history and palpation findings in patients with acute chest pain (Submitted).

Paper IV

Paper V

Copies of these papers are appended to this manuscript.
Acknowledgements
I wish to express my appreciation and thanks to my supervisors and everybody who has been involved in this project.

In particular, I wish to thank:

*Henrik Wulff Christensen*, project supervisor, on whose shoulder I have been leaning since I started in research. I wish to thank him sincerely for believing in my potential from the beginning, for many critical and constructive discussions, and for opening doors enabling this unique research collaboration. His impressive body of work laid the foundation for this thesis.

*Jan Hartvigsen*, principal supervisor, to whom I want to express my profound gratitude for his enthusiasm and optimism, never failing support and his readiness for constructive critical advice every step of the way.

*Werner Vach*, for his excellence in planning and analysing this project. I am deeply appreciative of his unique insight and perspectives in methodologies reaching far beyond statistical issues, and for his patience and kind guidance when faced with the pitfalls of research.

*Poul Flemming Højland-Carlsen*, for initiating a visionary project, providing constructive criticism and moral support.

*Torben Hagfelt*, for introducing me to the exciting world of cardiology, and for believing in this project, not for his own benefit, but for the benefit of patients.

*Jytte Johannesen*, from the Nordic Institute of Chiropractic and Clinical Biomechanics for her excellent and invaluable management of data collection. I am grateful for her warmth, her ever-present positive attitude and her support during the time when we shared the same office.

Furthermore, I would like to thank the observers in the repeated measures study, *Mads Hostrup Brunse, Alice Kongsted, Erik Poulsen and Thomas Nielsen* for their commitment, endless patience and interesting discussions.

I pass on special thanks to the four chiropractic clinics involved in the project without whose participation and positive attitude the clinical trial would not have been possible:
- Chiropractic Clinic in Nyborg (Henrik Wulff Christensen & Peter Højgaard)
- Hartvigsen & Hein Chiropractic Clinic in Odense (Lisbeth Hartvigsen & Tina Hein)
- Chiropractic Clinic in Odense (Charlotte Beck, Jess Wiberg & Grethe Thøstesen)
- Chiropractic Clinic in Svendborg (Hanne Nøddeschou-Fink & Svend Lund)

I want to thank all my colleagues at the Nordic Institute of Chiropractic and Clinical Biomechanics and Institute of Sports Sciences and Clinical Biomechanics for moral support and encouragement.
during my PhD, especially, Ulla Dinesen for administrative assistance and Henrik Hein Lauridsen for help with data analysis and constructive advice.

I would also like to thank the staff members of the Department of Cardiology and Department of Nuclear Medicine for their support and kind assistance, especially Tina Godskesen and the ‘Heart group’ for taking good care of my patients, and Anne Lerbjerg Nielsen for constructive discussions and invaluable assistance in matters related to cardiology and nuclear medicine.

The project was generously supported by the (Danish) Foundation of Chiropractic Research and Post Graduate Education; the Faculty of Health Sciences, University of Southern Denmark, Odense; the Nordic Institute of Chiropractic and Clinical Biomechanics; the Department of Nuclear Medicine and the Department of Cardiology, both at Odense University Hospital, Denmark.

**Dedication**

The PhD thesis is dedicated to my two children, Rasmus and Kristine, and my husband Morten. Morten’s never failing loving support, patience and encouragement made this possible.
TABLE OF CONTENTS

1. INTRODUCTION .......................................................................................................................... 8
   1.1 Abbreviations ............................................................................................................................ 9
2. OBJECTIVES ................................................................................................................................. 10
3. BACKGROUND ............................................................................................................................. 12
   3.1 Causes of chest pain .................................................................................................................. 12
      3.1.1 Acute Coronary Syndrome ................................................................................................. 12
      3.1.2 Angina pectoris ................................................................................................................ 12
      3.1.3 Non-cardiac chest pain ..................................................................................................... 13
      3.1.4 Musculoskeletal chest pain ............................................................................................... 13
      3.1.5 Segmental dysfunction of the neck and thoracic spine and cervicothoracic angina ............. 14
      3.1.6 Differential diagnoses ...................................................................................................... 14
   3.2 Mechanisms of referred pain .................................................................................................... 15
   3.3 Prevalence of chest pain ........................................................................................................... 15
      3.3.1 Prevalence of musculoskeletal chest pain ......................................................................... 16
   3.4 Natural history .......................................................................................................................... 16
   3.5 Diagnosis .................................................................................................................................. 17
      3.5.1 Diagnosis of acute coronary syndrome .............................................................................. 17
      3.5.2 Diagnosis of angina pectoris .............................................................................................. 17
      3.5.3 Diagnosis of segmental dysfunction and cervicothoracic angina ......................................... 18
   3.6 Spinal manipulative therapy for musculoskeletal chest pain ...................................................... 19
      3.6.1 Chiropractic therapy ...................................................................................................... 19
4. METHODS ...................................................................................................................................... 21
   4.1 Study population ....................................................................................................................... 21
   4.2 Variables ................................................................................................................................... 23
      4.2.1 Questionnaires .................................................................................................................... 23
      4.2.2 Outcome measures .......................................................................................................... 23
      4.2.3 Predictors of outcomes ..................................................................................................... 23
   4.3 Clinical assessment ................................................................................................................... 25
   4.4 Myocardial perfusion scintigraphy ............................................................................................ 25
   4.5 Interventions ............................................................................................................................. 27
      4.5.1 Chiropractic therapy ...................................................................................................... 27
      4.5.2 Self-management .......................................................................................................... 27
   4.6 Statistics and data analyses ...................................................................................................... 27
1. INTRODUCTION

This thesis is based on a previous work on patients with known or suspected, stable angina pectoris. In 2004, Christensen et al. reported on a standardised clinical examination protocol to screen these patients with chronic chest pain for musculoskeletal causes and introduced the term cervicothoracic angina (CTA) to define chest discomfort originating from the cervical spine or the thorax.\(^1\) As a cornerstone of diagnosis, systematic manual palpation of the cervical and thoracic spine, chest wall and thoracic paraspinal muscles was applied in combination with a detailed case history to assist in reaching a diagnosis of CTA. The examination protocol was tested for reliability and indirectly for validity using myocardial perfusion scintigraphy (MPS).\(^1\)-\(^4\) Additionally, a diagnostic algorithm tool was suggested to serve as an example of how to base the diagnosis of CTA on an objective and reproducible procedure, facilitating its use.\(^1\) Finally, a non-randomised clinical trial of chiropractic treatment for patients with CTA was conducted, and results indicated that chiropractic treatment may indeed be a beneficial treatment approach in these patients.\(^5\) The non-randomised design of the treatment study had obvious limitations and the use of the examination protocol was restricted to secondary sector patients, but the overall positive results unequivocally called for further investigation in wider clinical settings.

The vision of this thesis was to continue the existing work in terms of assessing the diagnostic procedures of musculoskeletal chest pain and to evaluate the potential benefit of manual treatment in patients with acute chest pain and suspected, but undocumented, acute coronary syndrome.
### 1.1 Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACS</td>
<td>Acute coronary syndrome</td>
</tr>
<tr>
<td>AMI</td>
<td>Acute myocardial infarction</td>
</tr>
<tr>
<td>AP</td>
<td>Angina pectoris</td>
</tr>
<tr>
<td>CAD</td>
<td>Coronary artery disease</td>
</tr>
<tr>
<td>CAG</td>
<td>Coronary angiography</td>
</tr>
<tr>
<td>CCS</td>
<td>Canadian Cardiovascular Society</td>
</tr>
<tr>
<td>CARPA</td>
<td>Non-cardiac chest pain evaluation and treatment study</td>
</tr>
<tr>
<td>CTA</td>
<td>Cervicothoracic angina</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>GERD</td>
<td>Gastro-oesophageal reflux disease</td>
</tr>
<tr>
<td>HVLA</td>
<td>High velocity low amplitude</td>
</tr>
<tr>
<td>IHD</td>
<td>Ischemic heart disease</td>
</tr>
<tr>
<td>MPS</td>
<td>Myocardial perfusion scintigraphy</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>Non-ST elevation myocardial infarction</td>
</tr>
<tr>
<td>REMUC</td>
<td>Reproducibility of the examination protocol for musculoskeletal chest pain</td>
</tr>
<tr>
<td>ROM</td>
<td>Range of motion</td>
</tr>
<tr>
<td>SMT</td>
<td>Spinal manipulative therapy</td>
</tr>
<tr>
<td>STEMI</td>
<td>ST-elevation myocardial infarction</td>
</tr>
<tr>
<td>UAP</td>
<td>Unstable angina pectoris</td>
</tr>
</tbody>
</table>
2. OBJECTIVES

The overall objective of the present work was to study the diagnosis and treatment of acute, musculoskeletal chest pain in the form of CTA in patients with suspected but undocumented ACS admitted to an emergency cardiology department. Specifically, the following research questions are investigated:

1. What is the prevalence of various diagnoses and clinical characteristics in patients with acute chest pain, and how do they compare in patients with and without ischemic heart disease?

2. What is the proportion of patients discharged from the emergency cardiology department whose chest pain is of musculoskeletal rather than cardiac origin?

3. What is the prevalence and character of musculoskeletal chest pain in these patients, and what is the cardiac status with respect to ischemic heart disease?

4. What are the most important determinants from the case history and clinical examination that influence the decision-making process of the chiropractor when assessing patients with chest pain, and is it possible to create a diagnostic rule tool for identification of musculoskeletal chest pain in the acute clinical setting?

5. How does a previously established decision tree for a patient with chest pain perform in a population of patients with acute chest pain?

6. Using MPS as an indirect measure, what is the validity of the musculoskeletal chest pain diagnosis?

7. Is the inter-observer agreement of decisions based on an examination protocol to evaluate musculoskeletal chest pain acceptable at a clinically relevant level?

8. What is the relative effectiveness of two conservative treatment approaches as examples of usual care for patients with musculoskeletal chest pain?

This thesis consists of five manuscripts, dealing with one or more of the research objectives mentioned above. The first question is addressed in a cross-sectional study using patient file data of consecutive patients admitted to an emergency cardiology department (Paper II). Questions 2-5 are addressed in a prospective, population-based, diagnostic evaluation study using a cohort of patients from the same emergency cardiology department (Paper III). Question 6 is addressed in the present thesis. Question 7 is addressed in a repeated measures design using a subset of the above-mentioned cohort (Paper IV). Question 8 is addressed in a single-blinded, randomised controlled trial using a
different subset of the above-mentioned cohort (Paper V). Methodological considerations and rationale for the study protocol are presented separately (Paper I).

It was not the purpose of this thesis to describe the mechanisms of ACS or AP in detail, as it was not the objective to describe in particular the rationale for MPS or the theoretical and biomechanical rationale for the manual therapy applied. Nor was it an aim to describe the diagnosis and treatment of other non-cardiac chest pain aetiologies.
3. BACKGROUND

3.1 Causes of chest pain
Chest pain is one of the cardinal manifestations of acute coronary syndrome (ACS) and accounts for 5-8% of admissions to the emergency department of a hospital. However, such pain may originate not only from the heart, but also stem from a variety of other causes - pulmonary, musculoskeletal, gastrointestinal, psychiatric, and dermatological. Some of these causes may result in serious, life threatening disease, whereas others are of a more benign nature. Perhaps with this in mind, elucidation of the cause of chest pain continues to present challenges to a variety of clinicians.

3.1.1 Acute Coronary Syndrome
Acute Coronary Syndrome (ACS) refers to any constellation of clinical symptoms that are compatible with acute myocardial ischemia (AMI). It encompasses,

- AMI with ST-segment elevation seen in an electrocardiogram (ECG) (STEMI)
- AMI with non-ST segment elevation seen in an ECG (NSTEMI)
- Unstable angina pectoris (UAP)

The clinical symptoms of ACS are mostly a complaint of prolonged chest pain or discomfort, severe epigastric pain with components typical of myocardial ischemia such as central compression or crushing chest pain, unexplained indigestion or belching, radiating pain to the neck, jaw, shoulders, back, or arms. It may also be associated with dyspnea, nausea and/or vomiting, and diaphoresis. In addition, persistent shortness of breath, weakness, dizziness, light-headedness, or loss of consciousness may be signs of ACS. UAP is characterised by pain during rest or by minimal exertion, or by increased intensity, frequency and duration of pain episodes in patients with known chronic, stable ischemic heart disease (IHD). The most common cause of ACS is reduced myocardial perfusion that results from coronary artery narrowing caused by a thrombus that developed on a disrupted atherosclerotic plaque. Occlusion of the coronary artery may be imminent, intermittent or persistent.

3.1.2 Angina pectoris
Stable angina is a clinical syndrome characterised by recurring discomfort in the chest, jaw, shoulder, back, or arms. Duration of discomfort is brief, usually less than 10 minutes. It is now usual to confine the term to cases in which the syndrome can be attributed to myocardial ischemia, although essentially similar symptoms can be caused by other disorders. Angina Pectoris (AP) is usually brought on by exertion or emotional stress and is associated with a disturbance in myocardial function, but without myocardial necrosis. It is caused by an imbalance between myocardial oxygen supply and consumption most commonly due to obstruction of the coronary arteries by atheromatous plaques.
According to the Danish Society of Cardiology and Danish Society of Thoracic Surgery, operational criteria for AP are:

- Retrosternal or precordial pain/discomfort, potentially radiating to the neck, jaw, upper extremity or back, lasting from a few minutes up to 10-15 minutes.
- Pain/discomfort provoked by low temperature, exertion or emotional stress.
- Pain/discomfort usually relieved by rest or nitroglycerin.\(^\text{16}\)

Typical AP meets all three criteria, atypical angina meets two of the above criteria, and non-cardiac chest pain meets one or none of the typical angina characteristics. When frequency, severity and duration of AP are unchanged over time, the term stable AP is used.\(^\text{17}\)

3.1.3 Non-cardiac chest pain
The cause of chest pain in patients with normal coronary anatomy remains an enigma. Even after extensive investigations, primarily of the cardiovascular or gastrointestinal systems, a sizeable minority are never diagnosed nor given a plan for follow-up.\(^\text{10,18-21}\) The residual group of patients presenting with symptoms indicative of ACS, but without ACS, are often given a provisional diagnosis of a non-ACS cardiovascular condition or a non-cardiac condition with another specific disease, but a fraction of them remain undiagnosed, i.e. they have non-specific chest pain or undifferentiated chest pain.

3.1.4 Musculoskeletal chest pain
The musculoskeletal system is recognised as a possible source of pain in patients with undifferentiated chest pain.\(^\text{10,14,22-25}\) It may be the main cause or a contributing cause of pain in the presence of cardiac or non-cardiac chest pain. The broad term of musculoskeletal chest pain comprises many different musculoskeletal causes and proposed pain mechanisms including mechanical, degenerative, traumatic, and inflammatory causes, but definitions and terms overlap (Table 1). Commonly, for many of these conditions, the diagnosis is essentially based on history and clinical examination findings with the use of investigations to exclude other conditions, rather than to confirm the diagnosis.

**Table 1. Subgroups of musculoskeletal chest pain.**

<table>
<thead>
<tr>
<th>Cervicothoracic angina(^\text{1})</th>
<th>Myositis(^\text{26})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Segmental thoracic dysfunction(^\text{27,28})</td>
<td>Intercostal myalgia(^\text{29})</td>
</tr>
<tr>
<td>Costovertebral dysfunctions(^\text{30-33})</td>
<td>Pectoral myalgia(^\text{34})</td>
</tr>
<tr>
<td>Degenerative pathology of the spine(^\text{35-37})</td>
<td>Thoracic outlet syndrome(^\text{38})</td>
</tr>
<tr>
<td>Cervical angina(^\text{35,36,39-42})</td>
<td>Fibrositis(^\text{32})</td>
</tr>
<tr>
<td>Chest wall tenderness(^\text{43})</td>
<td>Fibromyalgia(^\text{44})</td>
</tr>
<tr>
<td>Chest wall syndrome(^\text{45,46})</td>
<td>Tietze’s syndrome(^\text{45})</td>
</tr>
<tr>
<td>Sternoclavicular disease(^\text{32})</td>
<td>Costochondritis(^\text{44})</td>
</tr>
<tr>
<td>Stress fractures(^\text{47})</td>
<td>Seronegative spondyloarthropathies(^\text{48})</td>
</tr>
<tr>
<td>Slipping rib(^\text{42})</td>
<td>Psoriatic arthritis(^\text{49})</td>
</tr>
</tbody>
</table>
3.1.5 Segmental dysfunction of the neck and thoracic spine and cervicothoracic angina

Originating from the posterior aspect of the chest wall, segmental dysfunction of the spine is perhaps one of the most under-diagnosed causes of musculoskeletal chest pain.\(^{50}\) In those cases, pain is caused by segmental joint dysfunction of the lower cervical (C4-C7) or upper thoracic spine (Th1-Th8) and adjoining structures causing referred pain to the anterior aspects of the chest wall.\(^{27,51}\) Excessive strain on the spinal joints after trauma, effort or false movement may lead to abnormal firing of nociceptive structures.\(^{50}\)

In the prospective clinical study of patients with chronic chest pain by Christensen et al.,\(^{1}\) the term CTA was used to include patients with segmental dysfunction, and clinical characteristics which could differentiate patients with CTA from patients without was established. The different pain descriptors appeared with similar frequencies in the two groups, except for ‘sharp’ pain, which was more frequent in the CTA positive patients, who also experienced symptoms for a shorter time and with less frequent episodes. Physical activity provoking pain was significantly less frequent in the CTA positive group, and patients suffered more often from self-reported neck pain, thoracic spine pain and shoulder/arm pain. In contrast to common beliefs, movement of the thorax was rarely found to provoke chest pain. Finally in the study by Christensen et al.,\(^{1}\) systematic classification of patients, according to international guidelines for type and severity of angina pectoris, appeared to be an important indicator for distinguishing patients with and without CTA. Type of angina pectoris was classified according to Diamond and Forrester,\(^{52}\) into classes of typical, atypical and non-cardiac chest pain, whereas severity was graded in four categories in accordance with the Canadian Cardiovascular Society (CCS).\(^{53}\) Non-cardiac pain and atypical AP was significantly more frequent in the CTA positive group. Additionally, there was a significant trend for a generally higher CCS class in the CTA negative group.

Pain caused by segmental dysfunction has been reported to be worst at rest or after prolonged sitting and with spinal rotation,\(^{27,50}\) but pain worse at rest was only reported in approximately a third of patients with chronic chest pain and does not appear to be a discriminating factor.\(^{1}\) Unlike in ischemic heart disease, activity may relieve pain.\(^{50}\) However, the opposite scenario with pain on physical activity and relief by rest may also be the case in up to 50% of the CTA positive patients.\(^{1}\) Paraspinal muscular tenderness is often present together with spinal joint dysfunction,\(^{27}\) and sometimes, pain may be reproduced by palpation of the spinal joints and related structures.\(^{50}\)

3.1.6 Differential diagnoses

Chest pain may originate from a variety of locations such as:

- Intrathoracic structures, including the aorta, pleura, oesophagus, diaphragm.
- Tissues of the neck and thoracic wall, including skin, thoracic muscles, cervicothoracic spine, costochondral junctions, sensory nerves, breasts.
- Subdiaphragmatic organs, including stomach, duodenum, gallbladder.\(^{14}\)

Pain of psychosocial origin may also exist.\(^{11}\) The neural complexity of the thoracic spine along with referred visceral pain leads to poor pain source location, making the differentiation of causes and diagnosis of chest pain difficult in these cases.\(^{54,55}\)
3.2 Mechanisms of referred pain

Different musculoskeletal structures of the spinal region are recognised as pain-producing in humans, and deep somatic structures, i.e. muscles, fasciae, ligaments, tendons, joint capsules and periosteum, are capable of producing referred pain to remote sites. The classic papers of Kellgren and Feinstein outline common patterns of quasi-segmental pain referral following irritation of thoracic and lumbar spinal somatic structures. Dysfunctional spinal segments tend to refer pain to a zone corresponding to the distribution of the segmental innervations of the deep structures. Several spinal segments refer pain to the anterior chest wall, and the thoracic zygapophyseal joints at segments T3-T9 can cause areas of intense provoked pain referring anteriorly, one segment inferiorly and slightly lateral to the joint injected. Only the costotransverse joints have been shown not to refer pain anteriorly. Thus, deep somatic spinal pain may present diagnostic and therapeutic problems, since this type of pain may be indistinguishable from pain arising from both intra-thoracic and sub-diaphragmatic organs.

The mechanisms responsible for pain referral from somatic structures to adjacent anatomical segments are not known in detail, but several theories have been suggested. The overall concept can be explained by the convergence theory. This theory maintains that afferent nerve fibres from the primary algogenic focus in one region converge in the spinal cord’s dorsal horns with afferent fibres from another region onto a common second order neuron in the dorsal horn, thereby allowing misinterpretation of the source of pain by the central nervous system. In a refinement of this theory, called the hyperexcitability theory, the referred pain occurs through cross connections between second order neurons supplying the different regions, but only when the input reaches a certain threshold.

Cardiac pain is essentially ischemic pain transmitted by afferent sympathetic nerve fibres and vagal nerve fibres. The sympathetic nerves have cell bodies in the dorsal root ganglia and synapse also on interneurons in the dorsal horn of the spinal cord. Interneurons that receive visceral pain are called viscerosomatic neurons. The visceral pain from the heart is transmitted via the 4-5 upper thoracic spinal segments as well as some cervical segments. The sensory impulses from the viscera of the thorax and from the body wall, however, share the same spinal segments, with convergence of visceral and somatic pain fibres on the same interneurons in the spinal cord, which may explain why visceral pain is often referred, i.e., why it is often perceived in somatic areas remote from its origin.

3.3 Prevalence of chest pain

Cardiovascular diseases are the leading cause for hospitalisation in Denmark. In 2002, a total of 90,000 patients were admitted to hospital with cardiovascular disease. Out of these, ACS accounted for approximately 25,000 admissions and AP for an additional 22,000 admissions. In Denmark, where patients with acute chest pain are admitted to emergency cardiology departments, approximately 1/3 is diagnosed with AMI, 1/3 is diagnosed with UAP, and 1/3 with non-ACS.
Results from Scotland indicate that the number of hospitalisations for suspected ACS increased by 41% from 1990 to 2000 due to a doubling of hospitalisations for AP and other causes of chest pain.\(^{64}\) This is in contrast to the number of hospitalisations due to ACS, which declined by about 30%.

The different causes of chest pain have been investigated to varying degrees. Obviously, ACS and AP have attracted the most clinical and research attention, although the relative importance of each category of chest pain has not as yet been adequately defined.\(^10\)

3.3.1 Prevalence of musculoskeletal chest pain
In contrast to the very exhausting reports of ACS and AP, epidemiological studies of musculoskeletal chest pain are few and they present an interpretative challenge because of the inconsistent use of terminology, and the variability of criteria from one study to the next. Often, authors of studies fail to define musculoskeletal chest pain or describe the investigative procedures resulting in the diagnosis. Those who do, mainly focus on the anterior chest wall, whereas studies of segmental dysfunction, i.e. dysfunction of the cervicothoracic spine and posterior chest wall, are poorly represented in the scientific literature.

Several studies have looked at the prevalence of musculoskeletal chest pain in coronary care units and emergency departments in patients with suspected ACS. In those patients without ACS, overall musculoskeletal chest pain has been evaluated in five studies.\(^{20,65-67}\) Its prevalence ranged from 3-23 %, ranking it as the most frequent cause of pain\(^20\) to ranking it fourth following chest pain of a cardiac nature of undetermined origin, gastrointestinal and pulmonary disease.\(^65\) Herlitz et al.\(^66\) looked at patients attending an emergency department and evaluated the difference in musculoskeletal chest pain prevalence between patients hospitalised and patients discharged directly, and found a significant difference of 4% versus 29%, respectively.

Additionally three studies have specifically defined subgroups and diagnostic procedures of musculoskeletal chest pain resulting in higher prevalence; almost 30% in patients without AMI.\(^{19,68,69}\) Segmental dysfunction has been reported to account for 14% of patients with musculoskeletal chest pain\(^19\) to 29% of patients with suspected AMI.\(^69\)

3.4 Natural history
The natural history and degree of symptom turnover of musculoskeletal chest pain are poorly understood. Studies addressing the long term course of patients with musculoskeletal chest pain have not been identified, but studies of patients with non-cardiac chest pain have addressed the issue. Although considered a benign condition, it seems that non-cardiac chest pain has the ability to critically intrude into daily life.\(^70\)

For patients with non-cardiac chest pain, conflicting evidence exists regarding mortality. Patients with non-cardiac chest pain and no risk factors for CAD have been estimated to have an excellent prognosis for survival,\(^65\) and patients with suspected CAD but no perfusion deficits assessed by MPS, have been estimated to have a one year risk of cardiac death or AMI of less than 1%.\(^71-73\) These findings have recently been questioned by a four-year follow-up study of patients with acute chest pain admitted to an emergency department.\(^74\) The mortality rates for those
diagnosed with chest pain of cardiac origin and those with non-cardiac origin were 11% and 5.5%, respectively; however, the difference was not statistically significant. In an earlier study, Wilhelmsen et al.\textsuperscript{75} found that mortality was high among male patients with chest pain who did not have AP, and Sehkri et al.\textsuperscript{76} found that patients with non-cardiac chest pain had lower event rates than patients with AP, but accounted for almost one third of all primary end points, i.e. cardiac death and ACS.

Recurrent episodes of pain are frequent and estimated to affect 50-90% of patients with non-cardiac chest pain.\textsuperscript{20;73;74;77;78} In these patients, pain intensity is described as moderate to severe and of a higher intensity than cardiac chest pain. Continued episodes of pain are associated with disability,\textsuperscript{79;80} work absenteeism,\textsuperscript{20;73;78;79;81} reduced quality of life in terms of mental health, vitality, depression and anxiety.\textsuperscript{73;74;82;83}

Rates of readmissions to hospitals are reported to account for 14% on one-year follow-up\textsuperscript{20} to 20% during a three-year follow-up.\textsuperscript{77;84} Tew et al. reported no difference in patients with or without IHD in terms of overall care-seeking behaviour from the healthcare system, but more emergency department visits for patients without IHD.\textsuperscript{82} After one year, 50% of patients in the study by Spalding et al. had undergone further investigation with a generally low yield (20%) of investigative procedures.\textsuperscript{20}

3.5 Diagnosis
In patients with acute chest pain the first priority is to diagnose whether ACS is present and subsequently treat this; secondly, to establish whether other potentially life threatening disease, such as pulmonary embolism or aortic dissection, is present. Current guidelines speak of angina as a rather clear cut symptom,\textsuperscript{15} although pain characteristics in patients with documented ACS appear to be indistinguishable from characteristics in patients with undocumented ACS.\textsuperscript{22;85}

3.5.1 Diagnosis of acute coronary syndrome
Diagnosis of ACS is based on clinical presentation of symptoms, change in specific cardiac biomarkers of ischemia (Troponin I or T and creatine kinase MB(mass)), ECG changes compatible with acute or persistent ischemia and supplementary picture diagnostics showing signs of decreased mass of viable myocardium or myocardium regional dyskinesia.\textsuperscript{17} In UAP, the diagnosis is primarily clinically-based on the case history; secondly transient ECG changes may support diagnosis.\textsuperscript{17} Importantly, initial presentation of symptoms cannot be used to differentiate between different kinds of ACS or non-ACS diagnoses.\textsuperscript{9;85;86} In addition, severity of symptoms and final outcome in patients with ACS are not directly related; age, gender, social and professional factors influence presentation of symptoms.\textsuperscript{87-90} Ultimately, diagnosis is based on further testing in terms of cardiac biomarkers, ECG changes and picture diagnostics.

3.5.2 Diagnosis of angina pectoris
Initial assessment with a detailed case history is the cornerstone of diagnosis of AP, including CCS classification, combined with physical examination and non-invasive testing including ECG, pharmacological stress imaging or exercise imaging. Risk factors of coronary artery disease (CAD)
play a significant role in assessing the patients and dividing them into groups of low, intermediate and high risk according to the likelihood of CAD. Response to medical therapy may be used for diagnostic purposes in a ‘trial and error’ fashion, and, in patients with severe pain episodes or in intermediate and high risk cases, coronary angiography (CAG) is indicated.\textsuperscript{15,17}

3.5.3 Diagnosis of segmental dysfunction and cervicothoracic angina

Manual therapy is most commonly associated with disorders that have their origin in patho-mechanical or patho-physiological alterations of the locomotor system and its synovial joints.\textsuperscript{91} As a result, manual therapy is based on assessment procedures that take into consideration both functional and structural alteration of the neuromusculoskeletal system and often include a strong element of manual palpation.\textsuperscript{91} Manual palpation of human joints is recognised as an essential skill by manual medicine disciplines and is used extensively by chiropractors,\textsuperscript{91} physical therapists,\textsuperscript{92} osteopaths,\textsuperscript{93} and some medical doctors.\textsuperscript{94} The overall concept of manual palpation is to palpate and challenge relevant musculoskeletal structures during either active patient motion or clinician-guided passive motion of the patient to evaluate patient response and/or joint dysfunction.

Segmental joint dysfunction is a clinical syndrome caused by disturbance of function affecting quality and joint range of motion without structural change. The definition embodies disturbances in function that can be represented by decreased motion, increased motion or aberrant motion.\textsuperscript{91} A diagnosis of joint dysfunction identifies local altered mechanics, but it does not identify the underlying nature of dysfunction.

Palpation procedures differ in their diagnostic aims:

- \textit{Static palpation} is variable manual pressure performed to assess bony alignment and soft tissue structure, as well as evaluate patient response (both verbally and non-verbally) and even reproduce pain (Figure 1).
- \textit{Motion palpation} is variable manual pressure performed during active or passive joint movements, and involves evaluation of joint movement through the entire passive range of motion (Figure 1).
  - \textit{Prone motion palpation} is manual pressure and joint evaluation performed in the neutral joint position to evaluate \textit{joint-play}.\textsuperscript{91}
  - \textit{Sitting motion palpation} is manual pressure and joint evaluation performed at the end of passive range of motion of the joint to evaluate \textit{end-play}.\textsuperscript{91}
This diagram represents joint motion of a spinal joint in one plane. Joint-play occurs in the neutral position, followed by active and passive ranges of motion (ROM). The passive ROM goes beyond the active ROM entering the joint’s elastic barrier. End-play is evaluated at the end of passive ROM. Beyond the anatomical limit, trauma results.

3.6 Spinal manipulative therapy for musculoskeletal chest pain

Reports of beneficial therapies for segmental dysfunction and chest pain consist primarily of case studies or are empirical in nature. Case reports of chiropractic intervention have been found to be effective in management of musculoskeletal chest pain, and a randomised controlled trial pilot study that compared SMT to a non-functional ultrasound placebo found that SMT was superior for treatment of mechanical thoracic spine pain.

Christensen et al. recruited patients from a population of patients with suspected stable AP and conducted a non-randomised trial comparing patients with CTA who were treated with SMT with patients without CTA who did not receive SMT. Approximately 75% of the CTA positive patients reported improvement in both pain and general health after treatment, compared with a statistically significant smaller proportion of 22% and 25%, respectively, of CTA negative patients. The results added to the impression that chiropractic treatment is a useful option for patients with CTA, but the design of the study had obvious limitations.

3.6.1 Chiropractic therapy

Chiropractors use a range of different treatment modalities, all of which are directed to remove or relieve patient symptoms as well as prevent recurrence of symptoms. Most treatment modalities are used in combination, and although most people associate chiropractors with spinal manipulation exclusively, modern chiropractic treatment is as such not synonymous with a specific treatment modality.

Spinal manipulation therapy (SMT) is a manual procedure directed towards the joints of the spine. In ‘high-velocity low-amplitude’ (HVLA) spinal manipulation, the clinician performs a short lever, controlled, dynamic manual thrust of low amplitude and high velocity, directed towards a specific vertebral segment. The indication for SMT is one or more joints displaying signs of dysfunction, and the procedure acts on the various components of the vertebral motion segment. Often this procedure is accompanied by an audible ‘crack’. The actual active mechanism
in manipulation is not fully understood, but most likely both mechanical and neurological elements are in play.\textsuperscript{99} Spinal manipulation is generally recommended for a variety of acute and chronic mechanical spine disorders.\textsuperscript{100,101} In addition to spinal manipulation, chiropractors use a variety of other modalities such as:

- Mobilisation, a manual procedure that, like manipulation, aims at stretching the joint past the active ROM.
- Soft tissue treatment of muscles, ligaments, tendons and fasciae, including massage, trigger point therapy, myofascial release techniques, stretching techniques.
- Exercise and training modalities.
- Advice and information.
- Dry needling of myofacial structures.
4. METHODS

4.1 Study population
All patients were recruited from the emergency cardiology department at Odense University Hospital in Denmark. In Paper II, case histories of all 758 consecutive patients admitted to the department from May to June 2004 were evaluated. In Papers III, IV and V, patients were recruited from a population of 305 who were admitted to the department from August 2006 to March 2008 with suspected ACS. All 305 patients had ACS ruled out and were then recruited into the study and assessed at baseline. Of those, 275 had MPS. One hundred and fifteen patients were eligible for the randomised controlled trial, and 80 patients took part in the repeated measures study. Figure 2 shows the allocation of patients in each study and Figure 3 shows the flow of participant in the trial. The Regional Ethics Committee of Vejle and Funen counties approved the study (ref. no. S-VF-20060002). The Danish Data Protection Agency granted permission for the databases (ref. no. 2006-41-6-542) and the studies were registered at www.clinicaltrials.gov (trial numbers NCT00373828 and NCT00462241). Informed consent was obtained from all people participating in the clinical studies.

**Figure 2.** Study population
Figure 3. Flow of participants through the study.

Assessed for eligibility (n=4433)

Excluded (n=4124)
- Not meeting inclusion criteria (n=3975)

Eligible for baseline evaluation (n=458)

Excluded (n=149)
- Refused to participate (n=50)
- Not able to contact (n=86)
- Did not show for appointment (n=13)

Baseline Evaluation (n=309)

Excluded from RCT (n=194)
- Not meeting inclusion criteria (n=190)
- Other reasons (n=4)

CTA negative (n=190)

Eligible for baseline evaluation (n=458)

Excluded (n=149)
- Refused to participate (n=50)
- Not able to contact (n=86)
- Did not show for appointment (n=13)

Baseline Evaluation (n=309)

Excluded from RCT (n=194)
- Not meeting inclusion criteria (n=190)
- Other reasons (n=4)

CTA positive (n=115)

Randomisation

Self-management (n=56)

Chiropractic treatment (n=59)

Myocardial perfusion scintigraphy (n=275)

Follow up 4 weeks (n=105)

Follow up 12 weeks (n=263)
4.2 Variables

4.2.1 Questionnaires
In order to identify the study sample in the retrospective study (Paper II), medical records of consecutive patients were reviewed. Using predefined checklists, data were extracted from these records. Checklists were adapted from the FUMU-MILES project by Dr. Christensen to allow for meaningful comparison of data across studies.\(^1\) Based on international guidelines and textbook recommendations of items to include in a detailed patient history to derive at or exclude a diagnosis of ischemic heart disease, items of patient demographics, pain characteristics, and risk factors for ischemic heart disease were selected.\(^9,13,14\) In addition, referral patterns, physical examination findings, results of additional testing, referral for any further testing after discharge and/or any treatment plans were also recorded, as well as diagnosis at the time of discharge.

In the prospective part (Paper III-V) both at baseline and follow up, the questionnaires from part II and the studies by Christensen et al.\(^1,5\) formed the basis for questionnaires in part. Included were also questions about marital status, education, work and amount of weekly physical exercise. For the patient interview, the original questionnaires were slightly adapted to accommodate acute episodes of pain instead of chronic, stable pain; most importantly, in the study by Christensen et al., outcome was assessed after six weeks and patients were asked about pain status during the previous 2 weeks. In the present study, follow-up was after 4 weeks and pain status was assessed for the last week. Additionally, to increase responsiveness of the self-perceived change in outcome, the ordinal scales were changed from 5-point to 7-point in the present study.

4.2.2 Outcome measures
The outcomes were measured by self-report questionnaires that were collected at baseline, after four weeks and 12 weeks. For a detailed description of outcome measures and time of collection, see paper I and Figure 4.
Primary outcome measures in the RCT:
- Level of worst chest pain during the last week (0 = no pain to 10 = the worst pain possible).
- Improvement in chest pain (‘much worse’ to ‘much better’).

Secondary outcome measures in the RCT:
- Levels of pain during the last week (0 = no pain to 10 = the worst pain possible) of chest pain ‘now’, and ‘average’ chest pain, thoracic spine pain, cervical spine pain, and shoulder/arm pain. To avoid misunderstandings, drawings of human figures indicating the relevant anatomical regions were provided to the patients.
- Improvement in general health (‘much worse’ to ‘much better’).
- Medical Outcomes Study Short Form 36-item Health Survey (SF-36).\(^102,103\)

Information about side effects was collected for the chiropractic treatment group by the treating chiropractor before and after each treatment session.

4.2.3 Predictors of outcomes
- Patient expectations of treatment effect (‘getting much worse’ to ‘getting much better’).
**Figure 4.** Evaluation, intervention and follow up procedures for patients in the prospective studies (Paper III-V). (Adapted from Perera et al. 2007104).

<table>
<thead>
<tr>
<th>Timeline</th>
<th>Participants: CTA negative</th>
<th>Participants: CTA positive (Chiropractic treatment group)</th>
<th>Participants: CTA positive (Self-management group)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (time = 0)</td>
<td>A B C D E</td>
<td>A B C D E</td>
<td>A B C D E</td>
</tr>
<tr>
<td>Determination of eligibility to RCT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Randomization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initiation of treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Approximately 2 weeks</td>
<td>H</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>4 weeks</td>
<td></td>
<td>B J K</td>
<td>B J K</td>
</tr>
<tr>
<td>12 weeks</td>
<td>B K</td>
<td>B J K</td>
<td>B J K</td>
</tr>
<tr>
<td>52 weeks</td>
<td>B K</td>
<td>B J K</td>
<td>B J K</td>
</tr>
</tbody>
</table>

**Symbol** | **Content**
---|---
A | *Questionnaire* completed by the patient including information on occupation, education, physical and lifestyle factors, and expectation of treatment outcome.
B | *Questionnaire* completed by patient including information on pain intensity, general health and baseline values for the outcome measures.
C | *Semi-structured interview*, including pain characteristics, comorbidities, the past medical history, height and weight, and risk factors of ischemic heart disease.
D | *General health examination*, including blood pressure and pulse, stethoscopy, abdominal palpation, neck auscultation, clinical signs of left ventricular failure, neurological examination of the upper and lower extremities, and orthopaedic examination of the neck and shoulder joints.
E | *Specific manual examination* of the muscles and joints of the neck, thoracic spine and thorax, including active range of motion, manual palpation for muscular tenderness on the anterior and posterior chest wall, and motion palpation of the cervical and thoracic spine.
F | *Therapy group*. Chiropractic treatment consisting of high velocity, low amplitude manipulation directed towards the thoracic and/or cervical spine in combination with joint mobilisation, soft tissue techniques, stretching, stabilising or strengthening exercises, heat or cold treatment, and advice.
G | *Advice group*. Advice is given in an approximately 15 minute session following the baseline assessment, and is directed towards promoting self-management.
H | *Myocardial perfusion scintigraphy*
J | *Global assessment*. Improvement in chest pain and general health is rated by the participants using 7-point Likert-scales using the categories: Much worse, worse, a little worse, no change, a little better, better, and much better.
K | *Health care costs/Cost-effectiveness analysis*. Direct health care costs, direct non-health care costs and indirect costs are used in the economic evaluation as an indicator of cost-effectiveness.
4.3 Clinical assessment
The same examiner interviewed patients and performed clinical examination at baseline. Standardised forms, with answers of either yes/no or predefined categories, were constructed to assist in all three parts of the clinical assessment, i.e. the semi-structured interview, the general health examination and manual examination of the spine and chest wall, and to ensure a consistent level of information across patients. The assessment comprised three parts:

- A patient interview focusing on the present and past episodes of chest pain, in terms of subjective feelings of pain (frequency, duration, localisation, precipitating and relieving factors), and risk factors of ischemic heart disease (IHD) (family history of IHD, smoking habits, blood cholesterol, hypertension, diabetes). In addition, specific questions were asked about past medical history and any symptoms of the lungs and gastrointestinal system. Type and severity of chest pain and cardiovascular performance were classified in accordance with Danish and international guidelines. \(^{16,22,53,105}\) Patient expectations of treatment benefits and self-reported height and weight were also noted.

- A general health examination were performed where patients had their blood pressure and pulse recorded, heart and lung stethoscopy performed, abdomen palpated, neck auscultated, and clinical signs of left ventricular failure noted. Neurological examination of the upper and lower extremities in terms of sensitivity to touch and pain, reflexes and muscle strength as well as orthopaedic examination of the neck and shoulders was performed in order to rule out nerve root compression syndromes.

- Finally, manual examination including four types of palpation was carried out:
  1. Sitting motion palpation of segmental end-play restriction in lateral flexion and rotation of the cervical and thoracic spine (C4-C7 and Th1-Th8). \(^4\)
  2. Motion palpation with the patient in a prone position for segmental joint-play restriction of the thoracic spine (Th1-Th8). \(^4\)
  3. Evaluation of segmental paraspinal tenderness of the thoracic spine (Th1-Th8) with the patient in a prone position. \(^4\)
  4. Manual palpation of muscular tenderness of 14 points on the anterior chest wall with the patient in the supine position. \(^3\)

After a short break, patients who took part in the repeated measures study (Paper IV) had the clinical examination part of the evaluation protocol performed another four times by the four observers in that study.

4.4 Myocardial perfusion scintigraphy
MPS was performed at the Department of Nuclear Medicine at Odense University Hospital approximately two weeks following baseline evaluation. This non-invasive test is designed to evaluate regional myocardial perfusion under rest and stress conditions. It involves the injection of a radioactive-labelled substance, which is absorbed by the myocardium and accumulates in
proportion to myocardial blood flow. Such substances are injected under stress as well as resting conditions, and images are obtained to define the regional distribution of radioactivity within the myocardium. Based on this information, stress images are compared with rest images. All patients firstly underwent stress imaging using pharmacological stress testing by adenosine infusion or alternatively physiological stress testing (bicycle ergometer), if adenosine was poorly tolerated or contraindicated (i.e. significant aortic stenosis, 2. and 3. degree AV-block, asthma or constrictive disorders of the lungs). Only in the case of abnormal MPS at stress, was additional rest imaging carried out at least two days later. This was done in order to minimise patient exposure to radiation.

In the case of abnormal findings in the MPS, defects were considered as either fixed (i.e. defects that are present at stress and unchanged at rest) or reversible (i.e. defects that are present at stress, but improved at rest). Studies combining fixed and reversible defects were categorised as reversible.

The diagnostic accuracy of the MPS has an estimated sensitivity and specificity for detecting significant coronary disease of 75% [CI(95%) = 66–82%] and 79% [CI(95%) = 73–84%], respectively, using CAG as reference standard. It is, however, important to realise the difference between the structural changes detected by CAG (i.e. coronary artery stenoses) and the physiological process of regional ischemia detected by (function) MPS.

In addition to evaluate the frequency of myocardial ischemia, we also used MPS as an indirect measure of validity for the CTA diagnosis. The idea was to look at the distribution of reversible defects in the CTA positive and negative patient, as only such defects in viable myocardium is pain generating. Ideally, we would detect a considerably lower frequency of abnormal scans in CTA positive patients compared to CTA negative patients, thus excluding myocardial ischemia as a cause of pain and giving indirect evidence to the CTA diagnosis.

**Figure 5.** Myocardial perfusion scintigraphy.

The upper rows are results of stress testing and the lower rows results of rest testing showing three stages of progressing myocardial ischemia (bright zones indicate fully perfused areas of the myocardium, dark zones indicate areas of diminished and no perfusion).
4.5 Interventions
Interventions are described in detail in Paper V.

4.5.1 Chiropractic therapy
Patients with CTA were randomised to receiving either chiropractic care or self-management. The chiropractic care was provided by local community chiropractors at four different clinics. The clinics were chosen based on location and personal knowledge of individual chiropractors and their level of experience. It was up to the discretion of the chiropractor to choose an appropriate treatment program for individual patients. Treatment was only standardised in terms of maximum number of treatments per week and overall, it had to include HVLA spinal manipulation of the cervicothoracic spine.

4.5.2 Self-management
Usual procedures at the emergency cardiology department for patients with suspected musculoskeletal chest pain include a short explanation of their symptoms and recommendations to do simple, rotation exercises with the shoulders and arms (‘swimming-type’-motion). To mimic this usual care, the self-management program was designed to be intentionally minimal in its approach in terms of time and resources. It differed slightly, however, from usual care regarding time spent with the individual participant (approximately 15 minute) and the individualised exercises instructed by a trained professional with expertise in this area.

4.6 Statistics and data analyses
Descriptive statistics and univariate analyses were used to describe the population in terms of clinical characteristics and to compare associations between these characteristics and patients with and without ischemic heart disease (Paper II).

In the diagnostic, prospective study (Paper III), the question of interest was upon which determinants from case history and clinical examination did the clinician base the final diagnosis of CTA. To analyse this, a recursive, stepwise approach in the tradition of constructing classification trees was used to assess the association of variables with the final CTA status. Variables were dichotomised; ordinal variables were changed to a series of binary variables considering all possible cut points, and continuous variables were changed to four binary variables using cut points referring to the 20, 40, 60 and 80 percentiles. Positive and negative predictive values were calculated and taken into consideration when evaluating the decision-making process of the clinician. The derived decision tree was compared to the reconstructed decision tree from the Christensen study.¹

In the MPS study, the distribution between CTA status and frequency of abnormal findings on the perfusion scans was calculated using $\chi^2$.

In the repeated measures study (Paper IV), Cohen’s kappa was used to calculate reliability for binary examination variables, and an interclass correlation coefficient (ICC) was used to calculate continuous variables. A clinically acceptable cut point was arbitrarily defined at Kappa equal to or above 0.60.
In the randomised controlled trial (Paper V), analyses were based on the intention-to-treat principle and baseline differences in the outcome measures were taken into account in the analyses of group differences. Although randomisation yielded two statistically comparable groups at baseline, non-statistically significant differences in the baseline values of outcome measures between groups could be observed. It was expected that the outcome would be related to the baseline measurement, and, therefore regression models were used, in which the imbalance is of no consequence, to calculate both unadjusted and adjusted results. Per protocol analysis, excluding all patients with deviations from the protocol, and as treated analyses were performed repeating the original analyses.

Throughout the papers and this thesis $p < 0.05$ was considered statistically significant. Analyses were performed using STATA (Stata Statistical Software: release 9.2. Stata Corp, College Station, TX, USA).
5. RESULTS

5.1 Retrospective study
In total, 705 individuals were admitted to the emergency cardiology department and accounted for 420 (55%) episodes of chest pain (Paper II). Sixteen percent of patients had ACS. In patients without ACS, only 47% were given a diagnosis, with angina pectoris (AP) being the most common (30%). The prevalence of musculoskeletal and oesophago-gastro-intestinal conditions was low with 3% in each category. In all subgroups, recurrent pain episodes (43-58%) and readmissions to the hospital (37-56%) were frequent. It was not possible to identify statistically significant differences between patients with or without ACS in relation to the patient history, pain descriptors, aggravating or relieving factors, duration and frequency of pain, or risk factors of ischemic heart disease. In the majority of categories, only few data were provided in the patient files resulting in very small groups available for analysis.

5.2 Prospective diagnostic trial
A total of 302 patients were included in this part of the trial (PaperIII). Thirty eight percent (n=115) were diagnosed with CTA. The Mean age of participants was 52 years, with more than half of them male (56%). Overall the two groups were very similar in terms of pain characteristics and only a few indicators meaningfully discriminated CTA positive and CTA negative patients, including ‘sharp’ pain, gradual onset of pain, onset not related to meals, pain provoked by movement of upper body, and pain relieved by pain killers, all of which were more likely to occur in CTA positive patients. Comparing SF-36 scores for the study population with the scores in a reference population of healthy Danes aged 45–54 years, showed significantly lower scores in the study population for all eight domains (Figure 6).

Figure 6. Standardised quality of life scores (SF-36) in the entire population (n=302).

The extended box-plot shows medians, quartiles and outliers. The right whisker represents maximum values. The left whisker indicates minimum values or, in case of outliers, 1.5 times the inter-quartile range. Dots denote outlier values. A value of 0 indicates a score equal to that of the background population mean, a negative value indicates a lower and positive value and by inference, a higher quality of life.
Testing the performance of the four-step decision tree for patients with stable angina pectoris proposed by Christensen et al. yielded incorrect separation of 60% of patients.

The main determinants in the decision-making process of the clinician could be identified giving rise to a five-step classification tree for patients with an acute chest pain episode that would correctly classify 93% of patients. Using the top 13 indicators (Table 2) in step I-III encompassing simple indicators of palpation and the case history, resulted in classification of 64% of patients of which 95% were classified correctly. Palpation findings of the anterior and posterior chest wall were the most important indicators of a CTA diagnosis demonstrating very high negative predictive values.

Table 2. Accuracy statistics for step I-III individual indicator variables from the decision tree associated with a CTA positive diagnosis in the entire population (n=302).

<table>
<thead>
<tr>
<th>Indicator</th>
<th>CTA pos. n=112</th>
<th>CTA neg. n=190</th>
<th>Pos. predictive value</th>
<th>Neg. predictive value</th>
<th>OR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biomechanical dysfunction</td>
<td>112 (48.3)</td>
<td>120 (51.7)</td>
<td>0.48</td>
<td>1.00</td>
<td>∞ [16.94; ∞]</td>
</tr>
<tr>
<td>3 or more of the 5 palpation findings</td>
<td>111 (99.1)</td>
<td>124 (65.3)</td>
<td>0.47</td>
<td>0.99</td>
<td>59.08 [9.80; 2388.9]</td>
</tr>
<tr>
<td>Muscular tenderness on anterior chest wall</td>
<td>109 (97.3)</td>
<td>107 (56.3)</td>
<td>0.51</td>
<td>0.97</td>
<td>28.18 [8.81; 142.52]</td>
</tr>
<tr>
<td>Palpation of costa 4 reproduces pain</td>
<td>36 (32.1)</td>
<td>3 (3.2)</td>
<td>0.86</td>
<td>0.71</td>
<td>14.53 [5.70; 43.15]</td>
</tr>
<tr>
<td>Anterior muscular tenderness or costosternal junctions/xiphoid process tenderness</td>
<td>110 (98.2)</td>
<td>134 (70.5)</td>
<td>0.45</td>
<td>0.97</td>
<td>22.99 [5.80; 197.43]</td>
</tr>
<tr>
<td>&gt; 1 painful or 2 tender spots on anterior muscles</td>
<td>93 (83.0)</td>
<td>76 (40.0)</td>
<td>0.55</td>
<td>0.86</td>
<td>7.34 [4.03; 13.74]</td>
</tr>
<tr>
<td>Costosternal junctions/xiphoid process tenderness</td>
<td>102 (91.1)</td>
<td>109 (57.4)</td>
<td>0.48</td>
<td>0.89</td>
<td>7.58 [3.64; 17.21]</td>
</tr>
<tr>
<td>Palpation of costa 5 reproduces pain</td>
<td>27 (24.1)</td>
<td>9 (4.7)</td>
<td>0.75</td>
<td>0.68</td>
<td>6.39 [2.75; 16.04]</td>
</tr>
<tr>
<td>Angina pectoris, uncertain or negative</td>
<td>109 (98.2)</td>
<td>155 (82.5)</td>
<td>0.41</td>
<td>0.94</td>
<td>11.60 [2.85; 101.30]</td>
</tr>
<tr>
<td>Intercostals muscle 5 tenderness or pain</td>
<td>68 (60.7)</td>
<td>59 (31.1)</td>
<td>0.54</td>
<td>0.75</td>
<td>3.43 [2.05; 5.76]</td>
</tr>
<tr>
<td>Pain worse on movement of torso</td>
<td>32 (28.6)</td>
<td>16 (8.4)</td>
<td>0.67</td>
<td>0.69</td>
<td>4.35 [2.16; 8.96]</td>
</tr>
<tr>
<td>Pain relief on pain medication</td>
<td>25 (22.3)</td>
<td>13 (6.8)</td>
<td>0.66</td>
<td>0.67</td>
<td>3.91 [1.82; 8.72]</td>
</tr>
<tr>
<td>Pain did not start during a meal</td>
<td>109 (97.3)</td>
<td>168 (88.4)</td>
<td>0.39</td>
<td>0.88</td>
<td>4.76 [1.37; 25.32]</td>
</tr>
</tbody>
</table>

Data are sorted by the lower boundary of the 95% confidence intervals [95% CI] of the odds ratios (OR).
5.3 Myocardial perfusion scintigraphy
Stress testing was performed in 275 patients (90.2%), whereas rest testing was performed in only 135 of these 275 patients (49.1%). There was no statistically significant difference between groups (Table 3) in terms of abnormal MPS findings.

Table 3. Results of myocardial perfusion scintigraphy.

<table>
<thead>
<tr>
<th>CTA pos</th>
<th>CTA neg</th>
<th>CTA Total</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=115)</td>
<td>(n=190)</td>
<td>(n=305)</td>
</tr>
<tr>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>93 (86.9)</td>
<td>139 (82.7)</td>
<td>232 (84.4) 0.86</td>
</tr>
<tr>
<td>Abnormal</td>
<td>14 (13.1)</td>
<td>29 (17.3)</td>
<td>43 (15.6)</td>
</tr>
<tr>
<td>Reversible defects</td>
<td>10 (9.4)</td>
<td>20 (11.9)</td>
<td>30 (10.9) 0.48</td>
</tr>
<tr>
<td>Irreversible defects</td>
<td>4 (3.7)</td>
<td>9 (5.4)</td>
<td>13 (4.7)   0.50</td>
</tr>
<tr>
<td>Missing</td>
<td>8</td>
<td>22</td>
<td>30</td>
</tr>
</tbody>
</table>

5.4 Reliability of the CTA diagnosis
The prevalence of musculoskeletal chest pain ranged from 43% to 47% as measured by the four observers. Inter-observer agreement was clinically acceptable amongst the chiropractors and overall amongst all examiners (K=0.73 and K=0.62, respectively), but the students (K=0.47) was below the threshold for acceptability (Table 4). For single items of the protocol, the average kappa for all examiner pairs ranged from 0.01 to 0.59. For the continuous data, ICC ranged from 0.52 to 0.93.

Table 4. Agreement of the CTA diagnosis presented as Kappa values and 95% confidence intervals.

<table>
<thead>
<tr>
<th></th>
<th>Chiropractor 2 (n=74)</th>
<th>Student 1 (n=80)</th>
<th>Student 2 (n=65)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chiropractor 1</td>
<td>0.73 [0.51; 0.86]</td>
<td>0.76 [0.56; 0.87]</td>
<td>0.43 [0.16; 0.64]</td>
</tr>
<tr>
<td>Chiropractor 2</td>
<td>-</td>
<td>0.72 [0.53; 0.85]</td>
<td>0.48 [0.23; 0.67]</td>
</tr>
<tr>
<td>Student 1</td>
<td>-</td>
<td>-</td>
<td>0.47 [0.24; 0.66]</td>
</tr>
</tbody>
</table>

31
5.5 Treatment effect

One hundred and fifteen patients were randomised into the two interventions. Both groups experienced decreases in pain intensity and the proportion of patients with pain, and increased positive self-perceived changes and SF-36 scores all reflected better health and wellbeing. Observed between-group significant differences were in favour of chiropractic treatment, at 4 weeks regarding primary outcome self-perceived change in pain (p=0.0013), and at 12 weeks with respect to primary outcome numeric change in pain intensity (p=0.022) (Figure 7). In addition, the majority of the non-significant trends were also in favour of the chiropractic treatment group.

Figure 7. Patients’ self-perceived change in pain at 4 and 12 weeks follow-up.

On average, Chiropractic patients were seen seven times by the treating chiropractors, received high velocity, low amplitude spinal manipulation together with trigger point therapy, massage and a variety of treatment modalities. Side effects were common, but transient and benign in nature. Results were robust, and the overall conclusion did not change following per protocol or as treated analyses. Patient expectations had no impact on the results.
6. DISCUSSION

6.1 Summary of main findings

- Eighty four percent of patients dismissed from the emergency cardiology department did not have ACS (Paper II). Only three percent were diagnosed with musculoskeletal chest pain. Due to missing data, a comprehensive description and comparison of chest pain symptoms between patients with and without ACS was not possible.
- Thirty eight percent of patients evaluated in the prospective part of this work had musculoskeletal chest pain in the form of CTA (Paper III).
- CTA positive patients were more likely to report pain that was sharp, had gradual onset, debut not related to meals, provoked by movement of upper body, and relieved by pain killers. They were also more likely to have positive palpation findings (Paper III). Abnormal perfusion scans were found in 13% of CTA positive and 17% of CTA negative patients, but the difference was not statistically significant.
- The major determinants for a CTA positive diagnosis were presence of positive findings in overall palpation categories, numbers of palpation findings and absence of indicators for cardiac chest pain (Paper III). Using these indicators in combination with indicators from the case history, a 5-step diagnostic tool for identification of musculoskeletal chest pain was suggested.
- The previously established decision tree performed at a moderate level, classifying correctly 60% of patients (Paper III).
- Due to the low prevalence of abnormal perfusion scans, MPS was not suitable as an indirect measure for validating the CTA diagnosis in this cohort.
- The inter-observer agreement of the CTA diagnosis was clinically acceptable at Kappa value of 0.73 in experienced observers (Paper IV).
- Both patients receiving chiropractic treatment and self-management information experienced decrease in pain, self-perceived positive changes and increases in SF-36 cores (Paper V). Observed between-group differences were in favour of the chiropractic treatment, at four weeks regarding the primary outcome self-perceived change in pain, at 12 weeks with respect to the primary outcome numeric change in pain intensity.

6.2 Retrospective study

Based on patient file data, a high proportion (84%) of patients without ACS were identified among sufferers of chest pain, with a large proportion of them readmitted to hospital (45%) (Paper II). These patients are poorly described in the literature in terms of pain characteristics and risk factors, just as they were in the medical files used in this study. It was possible to only partly describe the clinical characteristics of chest pain in this population, and comparison of subgroups of patients was hindered by lack of available data. This retrospective analysis was based on clinical data from a busy clinical routine in which acute situations are common. However, in such a routine, information not specifically needed for research purposes is sometimes not recorded and the emphasis may be placed primarily on cardiac related questions. This was found to be the case in this
study with information lacking in up to 50% of patients. Probably, measures such as improved interview techniques, increased awareness of the problem combined with more systematic recording of findings and patient characteristics may significantly improve both clinicians and researchers’ capacity to classify these patients.

Looking specifically at patients in whom a musculoskeletal origin could be suspected, only one third of patients with non-ACS had chest wall palpation performed. Findings were abnormal in more than half of these, which indicated that 17% of all patients could have musculoskeletal chest pain, as opposed to the 3% actually given a musculoskeletal diagnosis. The 17% corresponds to data of previous research findings suggesting 7-23%. One of the reasons for this divergence may be explained by the fact that the department was reimbursed by the local county at a lower rate for a specific, as opposed to a non-specific, cardiac diagnosis, because the latter implied more extensive testing and thus a higher reimbursement.

6.3 Motive for the study design
Being a new area of research, many assumptions behind the rationale for the prospective part of this work was based on the experience of research on non-specific neck and low back. CTA is believed to be caused by neck and thoracic spine dysfunction and recent evidence indicates that there are many similarities in different spinal pain syndromes regardless of pain origin (i.e. cervical, thoracic or lumbar spine). In a population-based study estimating the prevalence of pain in the lumbar, thoracic and cervical regions of more than 30,000 Danish twins, the authors argue that thoracic spine pain with or without radiation to the chest wall shows patterns that are similar to those seen in patients with non-specific neck and low back pain with or without radiation to the extremities. The authors argue that thoracic spine pain may have a similar aetiology and natural course as that of neck and low back pain.

Despite focussing on patients with an acute episode of chest pain, this study also draws from the knowledge of chronic pain syndromes. In a study by How et al. of patients with various causes of musculoskeletal chest pain, the authors found many similarities between patients with musculoskeletal chest pain and patients with chronic pain. The majority of sufferers were females of middle age with other physical symptoms and a significant past medical history. High levels of anxiety and depression magnified symptoms and reduced patient-perceived well-being.

6.4 Population
In the current study, patients with an acute episode of chest pain were included, amongst whom were reports of both first time and repeated episodes. This was the case in both the retrospective (Paper II) and the prospective (Paper III) part of this study in which 50-60% of patients reported repeated episodes of pain. These findings are in concordance with previous reports.

Given the high proportion of patients with repeated episodes, some similarity, in terms of pain characteristics, palpation findings and cardiac classifications, was expected with the cohort of patients with suspected, stable AP described in the study by Christensen et al. Palpation findings, and to some degree pain characteristics, were similar between populations, but cardiac
classifications and SF-36 differed. This could in part be explained by overall population characteristics. In the cohort of patients with suspected, stable AP, referral for CAG was the main qualifier for participation in the study, which indicates that the chest pain episodes have most likely been consistent in frequency, severity and presentation to elicit referral. This consistent presentation of symptoms over time may have allowed for individuals to adapt to the situation both physically and mentally. This is in contrast to the current study, where the chest pain episodes were of such an acute and intense character that it led to admission to the emergency cardiology department. The acuteness of the situation and, in some case, fear provoking experience did not allow for adaptation of the situation of any kind.

In terms of treatment, the difference between patients with first time and repeated episodes of chest pain may have implications. Patients with recent onset and repeated symptoms do not respond equally well to spinal manipulative therapy and, therefore, should be managed differently. The small sample size in the current study, however, hindered subgroup analysis.

6.5 Myocardial ischemia
Abnormal MPS was found at a relatively low frequency of 16% of patients with no significant difference between CTA positive and CTA negative patients. Patients with normal MPS are at very low risk of future hard events (cardiac death and non-fatal MI), whereas a relationship between increasing extent and severity of scan abnormality and increasing hard event has been described in patients with abnormal scans. As is the case with patients in the current study, patients with mildly abnormal scans are at low risk of subsequent mortality but at intermediate risk for MI.

From a patient perspective, the frequency may, however, be a cause for concern. The patients had been assessed for coronary disease in the emergency cardiology department and, although some were referred for further cardiac testing, might therefore be expected to exhibit a distinctly lower coronary morbidity than the general population.

6.6 Other potential causes of chest pain
The examination protocol was not designed to classify or exclude other potential causes of non-cardiac chest pain, and thus, musculoskeletal chest pain could not be assumed as the sole cause of chest discomfort. Gastro-oesophageal reflux disease (GERD) is probably the most prevalent differential diagnosis, but owing to the lack of a ‘gold standard’ for the diagnosis of GERD, assessment of the sensitivity and specificity of these modalities is relatively limited. Generally, accepted definitions and procedures to describe and discriminate various types of chest pain are lacking and unsuccessful attempts were made to find systematic procedures to diagnose and differentiate between causes of non-cardiac chest pain, whether musculoskeletal, gastrointestinal, or a third type.

To complicate matters, unitary explanations are not always applicable to patients with non-cardiac chest pain. In the population of the current study, 13% of CTA positive patients had a dual diagnosis of ischemic heart disease, and anxiety and depression has been reported to be a major contributor to chest pain in patients with musculoskeletal chest pain. These causes may have
not only influenced the decision-making process in diagnosing CTA, but also influenced and limited the benefit of any treatment.

6.7 Clinical characteristics and the decision-making process
Historically, patients with chest pain have been sub-classified according to the quality of the pain,\textsuperscript{113} but recent reviews have demonstrated that these descriptors predicted acute myocardial infarction poorly or not at all.\textsuperscript{85,114} These conclusions were supported by the findings of this research (Paper III), in which sharp pain was the only pain descriptor which significantly increased the likelihood of a CTA diagnosis. Concordant with the results from Christensen et al.\textsuperscript{1}, palpation findings had very high associations with a CTA positive status, and the majority showed high negative predictive values indicating that absence of the indicator implied a CTA negative diagnosis.

In testing the performance of the decision proposed by Christensen et al.\textsuperscript{1}, many of the same indicators were identified as being highly associated with the CTA diagnosis and classification. Yet, the decision tree failed to correctly identify patients with clinically relevant accuracy. One major reason was the difference in prevalence of typical angina and the prevalence of certain palpation findings. However, it cannot be excluded that the failure may also have been caused by a difference in the use or weighting of criteria between clinicians in the two studies.

As observed in the study by Christensen et al.\textsuperscript{1}, reconstructions of the decision-making process was achieved through combinations of several indicators to form simple scores, and by combining these, it was possible to almost reconstruct the decision-making process. A ‘linear’ tree without ‘branches’ was produced, displaying a rather simple, hierarchical structure. At the top of the tree, the number of palpation findings and major palpation findings combined with the presence of AP were the main indicators followed by more specific palpation findings and items from the case histories.

When comparing the two decision trees, it was observed that the main indicators for a CTA positive diagnosis, i.e. pain on palpation of the anterior chest wall and cervicothoracic spine and absence of indicators for cardiac chest pain, were stable across different cohorts. However, several differences were also observed, and it was not possible to discriminate whether these differences were caused by clinician idiosyncrasies or differences in cohort characteristics. In any case, these results confirmed that caution should be noted before adopting complete classification systems in cohorts with different chest pain characteristics.

6.8 The reliability of the CTA diagnosis
Being essentially a clinical diagnosis, the syndromes of musculoskeletal chest pain are difficult to confirm and are susceptible to inter-observer variation. However, the perception remains that spinal palpation is a reliable procedure\textsuperscript{115,116} despite inconsistent evidence.\textsuperscript{117} The reason for this paradox may be the ‘face validity’ of palpation:\textsuperscript{116,118,119} the procedure makes sense intuitively and it seems to be a reasonable approach to identify spinal dysfunction. Furthermore, palpation appears to be a useful clinical tool in that it is non-invasive, easy to employ, inexpensive and risk-free.
The standardised examination protocol used in this study was created to support the decision process of diagnosing patients with musculoskeletal chest pain, results from the Christensen studies\textsuperscript{3,4} indicated that some elements of palpation had unacceptably low inter-observer agreement to allow for further use of the protocol in patients with chest pain. This led the authors to question the utility of parts of the thoracic spine examination, because poor reliability of some of the protocol items may hamper the ability of clinicians to diagnose and classify the musculoskeletal component of chest pain.\textsuperscript{3}

Results from a systematic review of the reliability of palpation suggested that observer agreement increased by using a combination of tests as usually done in overall patient assessment.\textsuperscript{117} This is confirmed by the results of the repeated measures study that indicated that experienced chiropractors can agree on the diagnosis of CTA at a clinically acceptable level (Paper IV).

Different words and schemes have been used to evaluate strength of reproducibility, but there are no guidelines for interpreting agreement\textsuperscript{120;121} and the clinical consequences of a given cut point for manual diagnoses are unknown. In studies of manual palpation, the level of acceptable clinical relevance has traditionally and somewhat arbitrarily been set at Kappa above 0.40,\textsuperscript{117} but given the potential of continued chest pain to critically intrude into daily life, Kappa greater or equal to 0.60 was chosen as acceptable in the present work.

6.9 The validity of the CTA diagnosis
One of the most important limitations of the present study is the lack of a reference standard against which to compare the CTA diagnosis. The decision tree was suggested to facilitate the CTA diagnosis, but the degree to which this diagnosis was actually correct is unknown.

The issue of verifying clinical manual diagnoses without reference standards has been addressed through various indirect measures such as mechanical models,\textsuperscript{122;123} pre- and post-manipulative changes,\textsuperscript{124;125} congenital block vertebrae,\textsuperscript{126} and zygapophysial joint injections\textsuperscript{127}

Christensen et al. chose to address the issue of validating the CTA diagnosis by using MPS as an indirect measure.\textsuperscript{1} In patients with CTA, 80% had normal myocardial perfusion compared with 50% in patients without CTA supporting that an experienced clinician could fairly convincingly identify a subset of patients with angina pectoris as having CTA.

Due to the low frequency of positive findings and lack of significant difference between CTA positive and negative patients (13% (n=14) and 17% (n=29), p=0.86, respectively), the value of MPS as an indirect measure of validity for the CTA diagnosis was limited in the present study. In the 14 CTA positive patients with perfusion abnormalities, five were classified with a dual diagnosis of possible AP and CTA. Four other patients had irreversible ischemia caused by previously undetected myocardial infarction. The observed frequencies of abnormal scans were considerably lower in the present cohort compared to the Christensen study. This was mainly caused by the study criteria that excluded patients with known ischemic heart disease from participation. Indirect support for the validity of the CTA diagnosis may, however, be found in positive response to treatment targeted at structures believed to be pain generators (muscles and joints of the cervicothoracic spine and chest wall),\textsuperscript{79} but further research is needed to confirm this.
6.10 Pain assessment
Within the field of cardiology, it has been common to classify type of chest pain into three categories in line with the Danish guideline, adopted from Diamond and into four classes defined by the Canadian Cardiovascular Society. However, there has been no tradition of recording a patient’s subjective feelings of pain intensity by the use of uni-dimensional scales (verbal rating scales, numeric rating scales, visual analogue scale or 11-point box scale). No single method can objectively record the pain intensity that the individual experiences. Nevertheless, in an attempt to systematically register the intensity of chest pain, use of box-scales was chosen. Box-scales have a definite number of pain levels, are practical to use, and have been shown to be as sensitive to changes in clinical pain as visual analogue scales. Additionally, they have been used extensively, amongst other things, for measurement of back and neck pain.

As recommended for studies of pain, several patient-rated variables were assessed. Pain intensity and self-perceived change in pain were chosen a priori as the primary outcomes, since these are considered the most important outcomes in patients with a variety of pain syndromes, along with quality of life. Global rating scales are regarded as clinically relevant and responsive to measuring patients’ perceived recovery.

Generally, there is uncertainty regarding the outcome measures of the non-disease specific measure of ‘pain’ and associated clinical implications. Retrospectively, the authors have come to realise that patients’ reporting of chest pain reflects both a sensory experience and the patient’s affective and cognitive responses. Accordingly, it might have been more useful to use a multidimensional scale, like the McGill pain questionnaire, which consists of three major classes of word descriptors – sensory, affirmative and evaluative – and has been developed to provide more comprehensive information about the subjective pain experience.

Fluctuation in pain is another issue that is difficult to address in research, and perhaps especially in pain syndromes with episodic pain. As demonstrated in the RCT (Paper V), the time point at which the participants are asked about symptoms and treatment effect is important. Pain perception appears to be a dynamic process and pain intensity and self-perceived change in pain may be rated independently of each other.

6.11 Interventions
In neck and low back pain caused by joint dysfunction, spinal manipulative therapy (SMT) is assumed to improve joint dysfunction, and is considered a beneficial treatment approach. In addition, case reports and a non-randomised trial have found chiropractic intervention effective in management of musculoskeletal-related chest pain.

We chose to undertake a randomised trial to identify the effect of chiropractic treatment compared to self-management, as these two pragmatic management strategies resembled usual conditions of care (Paper V). Procedures at the emergency cardiology department for patients with suspected musculoskeletal chest pain include a short explanation of their symptoms and recommendations to do simple rotation exercises with the shoulders and arms. To mimic this, the self-management program was designed to be intentionally minimal in its approach in terms of time and resources.
The pragmatic approach of this study was also reflected in the chiropractic treatment program. The treatment settings were local chiropractors’ offices with eight different chiropractors treating the group of participants. Observed effects were independent of a single, specific care provider, and, therefore, the findings may have more generalised validity, in particular because treatment was personalised and given at the discretion of each chiropractor. The pragmatic design of the current study, however, did not allow for standardisation of treatment or identification of active ingredients of the intervention, and we cannot exclude that the treatment effect in favour of the chiropractic treatment groups was not caused by provider attention.

In low back pain trials, patients classified using a system designed to guide treatment are treated more effectively than patients treated without regard to classification, and the sometimes discouraging results of different intervention studies have in part been attributed to lack of such classification. Participants in the current study were only eligible for randomisation if SMT was indicated, i.e., the patients had CTA. This enabled the initiation of a treatment directed towards the perceived origin of pain, rather than treating a symptom (e.g. chest pain) as criticised in the low back pain trials.

Both groups experienced reductions in pain intensity and positive self-perceived treatment effects, which could be the result of regression towards the mean, but we also observed a consistent tendency of results in favour of the chiropractic treatment group. Even though group differences were small, the improvement in pain intensity in both groups was substantial. One may argue that chiropractic treatment is an ‘add on’, perhaps leading to faster recovery than without treatment.

With the small group differences, study limitations, and unresolved issues in mind, the question remains whether active chiropractic treatment leads to faster recovery and is worth the additional cost. On the other hand, the scale of the problem in terms of number of patients concerned, the documented consequences in daily life and repeated contact to the health care system for those affected certainly justify intervention to minimize suffering and cost. In order to estimate the cost-effectiveness of the interventions, one year follow-up data from patients were collected alongside information of additional health care use of non-study providers and EuroQol 5D, and data are presently being evaluated.
7. CONCLUSIONS

- Using patient file data, we identified a high proportion (84%) of patients without ACS among sufferers of chest pain (Paper II). The quality and sparseness of the recorded were a limitation for describing the symptoms of chest pain in terms of pain characteristics and comparing major subgroups of patients.
- Musculoskeletal chest pain in the form of CTA was identified in 38% of patients evaluated in the prospective part of this work (Paper III).
- Only few characteristics from the case history increased likelihood of a CTA positive diagnosis, whereas palpation findings were a major discriminating factor between CTA positive and negative patients. Abnormal perfusion scans were found in a minority of patients in either group.
- In the presence of information on palpation findings and case history, a combination of several indicators was used when diagnosing CTA (Paper III). The major determinants for a CTA positive diagnosis were presence of positive finding in overall palpation categories, number of palpation findings and absence of indicators for cardiac chest pain (Paper III).
- Indicators of major and minor importance for a positive CTA status may be consistent across different cohorts, but transferring of complete classification scheme between those cohorts should not be undertaken uncritically (Paper III).
- The validity of the CTA diagnosis could not be assessed using MPS, but indirect support for the validity may be found in the positive effect of treatment directed towards perceived pain generating structures.
- Substantial agreement at a clinically acceptable level was found amongst experienced clinicians when evaluating CTA status (Paper IV).
- Results suggested that chiropractic treatment might be a valid therapeutic option in patients with acute chest pain of musculoskeletal origin, but further research in relation to patient selection, standardisation of interventions and identification of potentially active ingredients is needed (Paper V).
8. PERSPECTIVES

Musculoskeletal chest pain is a new area of research and the present study has fostered new information and ideas. These ideas have been drawn up in an agenda for future areas of research:

- Subgroups and operational criteria for diagnoses of different types of musculoskeletal chest pain should be established. Clear definitions should not only provide clinicians with the means to offer patients appropriate treatment but also provide patients with clear explanations for symptoms and prognosis. In relation specifically to patients with CTA, it remains to be indentified for whom chiropractic treatment or another intervention is most beneficial.
- Relevant MeSH words that adequately differentiate aspects of musculoskeletal chest pain should follow alongside such definition to guide clinicians and researchers in efforts of compiling knowledge in this area.
- Determinants for a CTA positive diagnosis should be evaluated in wider clinical settings, in cohort with different chest pain characteristics, and using multiple clinicians with different professional backgrounds.
- Importantly, the validity of the CTA diagnosis remains to be established. In the lack of a gold standard, one viable option may be to explore the relative treatment effect of chiropractic treatment in CTA positive and negative patients.
- Further research should focus on identification of responsive outcome measures. Clarification of what aspects of the pain episode patients consider important may be needed to identify such measures and to schedule appropriate treatment. This may be accomplished through patient interviews.
- We have explored the relative treatment effect of a personalised medicine approach, but standardisation of interventions and identification of potentially active ingredients may be needed.
- Finally, continued work should focus on finding other combinations of treatment either directed towards the musculoskeletal component of chest pain by itself, or in conjunction with treatment for competitive disorders causing chest pain.

Ultimately, the goal of research in non-cardiac chest pain is to develop an algorithm for the diagnosis and treatment of chest pain that is safe, effective and affordable. A mean to provide such an algorithm could be through the development of a ‘chest pain disability index’ in which a combination of different outcome measures could differentiate non-cardiac from cardiac aetiologies. The chest pain disability index could combine physical and psychological capacity. Obviously, such an index should be developed in collaboration with different medical specialties and manual therapy disciplines.

Musculoskeletal chest pain is only part of such a regimen, but improvement in the manual diagnosis as part of the enhanced differential diagnosis in non-cardiac chest pain disorders
would make an important contribution to obtaining meaningful, manageable and clinically relevant definitions of the different non-cardiac chest pain disorders.

As a result of the possibility to identify a subgroup of patients with chest pain who has in fact pain originating from the musculoskeletal system, the use of a case history and a standardised examination program should be advocated in general practice and at departments of cardiology by means of postgraduate courses. In consequence, a proportion of admissions and continued unnecessary diagnostic procedures might be avoided.
9. SUMMARY IN DANISH

Denne ph.d.-afhandling omhandler diagnostik og behandling af akutte brystsmerter afledt fra nakke, brystrygsøjle og brystvæggen, kaldet cervico-thorakal angina (CTA). De beskrevne patienter har været indlagt på et akut kardiologisk modtagelsesafsnit (KARMA) pga. mistænkt, men afkræftet akut koronar syndrom (AKS). Arbejdet består af to dele, et retrospektivt og et prospektivt, beskrevet i fem manuskripter (I-V). Rationale og metodiske overvejelser i det prospektive arbejde er beskrevet i manuskript I.

Formålet i den retrospektive del var at vurdere forekomsten af forskellige diagnoser og kliniske karakteristika relateret til patienter med brystsmerter på KARMA (II). I det prospektive arbejde ville vi belyse forekomsten af både iskæmisk hjertesygdom og CTA hos patienter med brystsmerter og beskrive den diagnostiske beslutningsproces, der leder til CTA diagnosen, når baseret på sygehistorie og klinisk undersøgelse (III). Derudover var det formålet at vurdere reproducerbarheden (IV) og validiteten af CTA diagnosen. Endelig ville vi vurdere, om patienter med CTA har gavn af kiropraktisk behandling (V).

I manuskript II undersøges kliniske karakteristika ved hjælp af medicinske journaler fra 758 patienter på KARMA. I delarbejde III undersøges 305 patienter fra samme sted ved baseline ved hjælp af en detaljeret anamnese, klinisk undersøgelse og manuel undersøgelse af nakke, ryg og brystvæg. Der blev udført myokardiescintigrafi for at vurdere omfanget af iskæmisk hjertesygdom og som indirekte mål for validiteten af CTA diagnosen. I manuskript IV blev overensstemmelsen mellem fire klinikeres CTA diagnose vurderet. Behandlingsdelen (IV) blev gennemført som et randomiseret, kontrolleret forsøg, hvor 115 patienter med CTA blev tilfældigt tildelt enten kiropraktisk behandling eller information efter ”lev-som-du-plejer” principippet.

Resultaterne af det samlede arbejde viser, at en kiropraktor kan identificere en undergruppe af patienter med CTA ved hjælp af systematisk manuel palpation af rygsøjlen og brystvæggen kombineret med anamnese, i det aktuelle materiale 38 %. Hos 87 % af denne gruppe blev der fundet normal perfusion i myokardiet mod 83 % i gruppen af CTA negative patienter. Det anvendte undersøgelsesprogram kan bruges af flere klinikere med en høj grad af overensstemmelse i den afledte diagnose, mens validiteten af programmet ikke kunne bestemmes. Endelig antydede behandlingsstudiet, at patienter med CTA kan have gavn af kiropraktisk behandling.

Sammenfattende gav projektet indtryk af, at muskuloskeletale dysfunktion kan være en (medvirkende) årsag til brystsmerter hos patienter med akutte brystsmerter, samt at kiropraktisk behandling kan være en behandlingsmulighed hos disse. De kliniske konsekvenser af det gennemførte behandlingsforsøg kan ikke drages, før der foreligger langtidsresultater og omkostningsanalyser.
10. SUMMARY IN ENGLISH

This is a PhD thesis on the diagnosis and treatment of acute chest pain arising from the musculoskeletal system, named cervico-thoracic angina (CTA). Described patients have been discharged from an emergency cardiology department (ECD) after an episode of suspected, but undocumented acute coronary syndrome (ACS). This thesis comprises a retrospective and a prospective part described in five manuscripts (Papers I-V). The rationale and methodological considerations behind this project were described in Paper I.

The aim of the retrospective part was to evaluate the prevalence of various chest pain diagnoses and clinical characteristics in patients with acute chest pain in an ECD setting (Paper II). The aim of the prospective part was to quantify the frequency of ischemic heart disease and CTA in patients with chest pain and to describe the diagnostic decision-making process when based on case history and clinical examination (Paper III). In addition we aspired to evaluate the reliability of the decision for detection CTA (Paper IV) and the validity of the diagnosis. Finally, we aimed at determining if patients with a CTA positive diagnosis would benefit from chiropractic treatment (Paper V).

In Paper II, we investigated the clinical characteristics of 758 patients with chest pain using medical file data. In Paper III, 305 patients were examined using case history, clinical examination and manual palpation of the spine and thorax. Myocardial perfusion scintigraphy was carried out to evaluate the frequency of ischemic heart disease and to indirectly assess the validity of the CTA diagnosis. In Paper IV, we investigated the inter-observer agreement between four observers diagnosing CTA. The intervention study was conducted as a randomised controlled trial in which 115 patients with diagnosed CTA were allocated to receive either chiropractic care or self-management (Paper V).

Results indicate that a chiropractor using systematic manual palpation of the spine and thorax in combination with the case history could identify a subgroup of 38% of patients with CTA. In this group, we found normal myocardial perfusion in 87% compared to 83% in the CTA negative group. It was possible to establish an examination procedure with low inter-observer variation, but the validity of the procedure could not be established. Finally, the intervention study suggested that patients with CTA might benefit from chiropractic treatment (Paper V).

In summary, the combined work suggests that musculoskeletal dysfunction can be a (contributory) cause of chest pain in patients with acute chest pain, and that manual therapy is a possible treatment for these patients. The clinical consequences of the intervention trial cannot be concluded before we have analysed the long-term results and cost-effectiveness.
11. REFERENCES


(22) Gibbons RJ, Abrams J, Chatterjee K, Daley J, Deedwania PK, Douglas JS et al. ACC/AHA 2002 Guideline update for management of patients with chronic stable angina. Available from:


(39) Nachlas IW. Pseudo-angina pectoris originating in the cervical spine. JAMA 1934;323-5.


(66) Herlitz J, Karlson BW, Lindqvist J, Sjolin M. Characteristics and long-term outcome of patients with acute chest pain or other symptoms raising suspicion of acute myocardial infarction in relation to whether they were hospitalized or directly discharged from the emergency department. Coron Artery Dis 2002; 13(1):37-43.


(97) Rabey MI. Costochondritis: Are the symptoms and signs due to neurogenic inflammation. Two cases that responded to manual therapy directed towards posterior spinal structures. Man Ther 2008; 13:82-86.


(100) Underwood M. Low back pain - Early management of persistent non-specific low back pain. NICE clinical guideline 88. Developed by the National Collaborating Centre for Primary Care. Available from: www.nice.org.uk/CG88 [last accessed May 2009]


(113) Chambers J, Bass C. Atypical chest pain: looking beyond the heart. QJM 1998; 91(3):239-244.

53


12. APPENDIX
A. Paper I
Study protocol

Diagnosis and treatment of musculoskeletal chest pain: design of a multi-purpose trial

Mette J Stochkendahl*1,2, Henrik W Christensen1, Werner Vach1,3, Poul Flemming Høilund-Carlsen4, Torben Haghfelt5 and Jan Hartvigsen1,2

Address: 1Nordic Institute of Chiropractic and Clinical Biomechanics, Part of Clinical Locomotion Science, Odense, Denmark, 2Institute of Sports Science and Clinical Biomechanics, University of Southern Denmark, Odense, Denmark, 3Department of Statistics, University of Southern Denmark, Odense, Denmark, 4Department of Nuclear Medicine, Odense University Hospital, Denmark, Odense, Denmark and 5Department of Cardiology, Odense University Hospital, Denmark, Odense, Denmark

Email: Mette J Stochkendahl* - m.jensen@nikkb.dk; Henrik W Christensen - h.wulff@nikkb.dk; Werner Vach - werner.v@stat.sdu.dk; Poul Flemming Høilund-Carlsen - pfhc@ouh.fyns-amt.dk; Torben Haghfelt - bente.wichmann@ouh.fyns-amt.dk; Jan Hartvigsen - jhartvigsen@health.sdu.dk

* Corresponding author

Abstract

Background: Acute chest pain is a major health problem all over the western world. Active approaches are directed towards diagnosis and treatment of potentially life threatening conditions, especially acute coronary syndrome/ischemic heart disease. However, according to the literature, chest pain may also be due to a variety of extra-cardiac disorders including dysfunction of muscles and joints of the chest wall or the cervical and thoracic part of the spine. The diagnostic approaches and treatment options for this group of patients are scarce and formal clinical studies addressing the effect of various treatments are lacking.

Methods/Design: We present an ongoing trial on the potential usefulness of chiropractic diagnosis and treatment in patients dismissed from an acute chest pain clinic without a diagnosis of acute coronary syndrome. The aims are to determine the proportion of patients in whom chest pain may be of musculoskeletal rather than cardiac origin and to investigate the decision process of a chiropractor in diagnosing these patients; further, to examine whether chiropractic treatment can reduce pain and improve physical function when compared to advice directed towards promoting self-management, and, finally, to estimate the cost-effectiveness of these procedures. This study will include 300 patients discharged from a university hospital acute chest pain clinic without a diagnosis of acute coronary syndrome or any other obvious cardiac or non-cardiac disease. After completion of the clinic’s standard cardiovascular diagnostic procedures, trial patients will be examined according to a standardized protocol including a) a self-report questionnaire; b) a semi-structured interview; c) a general health examination; and d) a specific manual examination of the muscles and joints of the neck, thoracic spine, and thorax in order to determine whether the pain is likely to be of musculoskeletal origin. To describe the patients status with regards to ischemic heart disease, and to compare and indirectly validate the musculoskeletal diagnosis, myocardial perfusion scintigraphy is performed in all patients 2–4 weeks following discharge. Descriptive statistics including parametric and non-parametric methods will be applied in order to compare patients with and without musculoskeletal chest pain in relation to their scintigraphic findings. The decision making process of the chiropractor will be elucidated and...
reconstructed using the CART method. Out of the 300 patients 120 intended patients with suspected musculoskeletal chest pain will be randomized into one of two groups: a) a course of chiropractic treatment (therapy group) of up to ten treatment sessions focusing on high velocity, low amplitude manipulation of the cervical and thoracic spine, mobilisation, and soft tissue techniques. b) Advice promoting self-management and individual instructions focusing on posture and muscle stretch (advice group). Outcome measures are pain, physical function, overall health, self-perceived treatment effect, and cost-effectiveness.

Discussion: This study may potentially demonstrate that a chiropractor is able to identify a subset of patients suffering from chest pain predominantly of musculoskeletal origin among patients discharged from an acute chest pain clinic with no apparent cardiac condition. Furthermore, knowledge about the benefits of manual treatment of patients with musculoskeletal chest pain will inform clinical decision and policy development in relation to clinical practice.

Trial registration: NCT00462241 and NCT00373828

Background
Acute chest pain is believed to be one of the most common reasons for hospital admission in Denmark [1,2]. Figures from the United States show that chest pain is the second most common reason for emergency department visits, accounting for 5.4% or more than 4 million visits per year [3]. The primary concern in these cases is of cause cardiac disease, but in about 50% of cases the aetiology appear to be non-cardiac [4,5], and in around 20% of the patients admitted to chest pain clinics no definitive diagnosis can be made [6].

Chest pain patients with normal coronary perfusion have an excellent prognosis for survival, and a future risk of cardiac morbidity similar to that reported in the background population [7-9]. However, about three quarters of patients with undiagnosed chest pain continue to suffer from residual pain with large personal and socio-economic consequences in terms of anxiety, fear of undiagnosed heart disease, loss of daily function and working capacity, and re-admissions to the hospital [10-16]. Chest pain differential diagnoses include primarily pulmonary, gastrointestinal, psychosocial, or musculoskeletal problems. Musculoskeletal problems alone accounts for 5–20% of the total number of admissions in acute chest pain clinics [16-18]. Hence, the musculoskeletal system is a recognized possible source of pain in patients with chest pain, even if no standardized criteria for the diagnosis exist at this point.

An extensive body of literature addresses patient assessment and management protocols for patients presenting with chest pain, but these focus primarily on cardiopulmonary [19-22], gastro-oesophageal [5,23], and psychological conditions [11,24,25], and protocols aiming at diagnosis of musculoskeletal chest pain remain scarce, and the effect of treatment strategies, including medical treatment (oral anti-inflammatory drugs), exercise (strength and/or stretching), advice, and manual approaches have not been evaluated. To our knowledge, only one non-randomized study deals with manual examination and treatment of patients with musculoskeletal chest pain [26,27]. In this study, an examination program consisting of a general health examination and a specific manual examination of the thorax and cervico-thoracic part of the spine was developed for a population of patients with suspected or known stable angina pectoris referred to a tertiary hospital for coronary angiography [26]. The examination program together with the detailed case history was applied by a chiropractor to make a diagnosis of discomfort from the musculoskeletal system, cervico-thoracic angina (CTA). In the absence of a true golden standard to validate the CTA diagnosis, myocardial perfusion scintigraphy (MPS) was used as a by proxy measure of validity with some success: Eighty percent of the CTA-positive patients had normal perfusion compared to 50% in the CTA-negative group. Moreover, results indicated that patients with CTA may benefit from chiropractic treatment.

We therefore decided to perform a multi-purpose clinical trial consisting of 1) a prospective, population-based, diagnostic evaluation study, 2) a single-blinded, randomized clinical trial (RCT), and 3) a cost-effectiveness analysis alongside the RCT.

The aims are:
• To determine the proportion of patients discharged from a university hospital chest pain clinic in whom their chest pain may be of musculoskeletal rather than cardiac origin. Specifically, we wish to determine the prevalence and character of musculoskeletal chest pain, and to describe cardiac status with respect to ischemic heart disease.
To investigate the diagnostic decision making process of a chiropractor in these patients, using MPS as an indirect measure of validity.

To determine the relative clinical effectiveness of chiropractic manual treatment versus advice directed towards promoting self-management using pain and patient-rated outcomes as primary outcome measures. Finally, we will estimate the cost-effectiveness of these procedures.

**Methods/Design**

This clinical trial is being conducted at Odense University Hospital in Odense, Denmark. The study began in 2006, and is ongoing. Approval has been granted by the regional ethics committee for Funen and Vejle Counties, Denmark, approval number #VF 20060002, and informed consent is obtained from all participants.

**Study population**

Three hundred consecutive patients with an episode of suspected non-cardiac acute chest pain are being recruited among patients discharged from an acute chest pain clinic situated at a large specialized cardiology department. All patients have undergone a standardized evaluation program at the chest pain clinic ruling out any obvious and significant cardiac or non-cardiac disease, including acute coronary syndrome. Following discharge from the chest pain clinic, all patient records are screened for the inclusion and exclusion criteria into the present study, and potential participants are contacted personally or by telephone and invited to participate.

**Inclusion/exclusion criteria**

The inclusion and exclusion criteria are presented in Table 1.

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>To be included in the project the participant must</td>
<td>Patients will not be included if any of the following conditions are present</td>
</tr>
<tr>
<td>- Have chest pain as their primary complaint.</td>
<td>- Acute coronary syndrome.</td>
</tr>
<tr>
<td>- Have an acute episode of pain of less than 7 days duration before admission.</td>
<td>- Previous Percutaneous Coronary Intervention or Coronary Artery Bypass Grafting.</td>
</tr>
<tr>
<td>- Consent to the standardized evaluation program at the chest pain clinic.</td>
<td>- Chest pain from other definite cause, cardiac or non-cardiac. The condition must be verified clinically during admission (i.e. pulmonary embolism, pneumonia, dissection of the aorta, ...).</td>
</tr>
<tr>
<td>- Have pain in the thorax and/or neck.</td>
<td>- Inflammatory joint disease.</td>
</tr>
<tr>
<td>- Be able to read and understand Danish.</td>
<td>- Insulin dependent diabetes</td>
</tr>
<tr>
<td>- Be between 18 and 75 year of age.</td>
<td>- Fibromyalgia.</td>
</tr>
<tr>
<td>- Be a resident of the Funen County</td>
<td>- Malignant disease.</td>
</tr>
<tr>
<td></td>
<td>- Apoplexy, dementia, or unable to cooperate.</td>
</tr>
<tr>
<td></td>
<td>- Major osseous anomaly.</td>
</tr>
<tr>
<td></td>
<td>- Osteoporosis.</td>
</tr>
<tr>
<td></td>
<td>- Pregnancy.</td>
</tr>
<tr>
<td></td>
<td>- Does not want to participate.</td>
</tr>
<tr>
<td></td>
<td>- Other — the reason for non-inclusion will be registered.</td>
</tr>
</tbody>
</table>

A record will be kept of the number of subjects excluded from the study, as well as those who are eligible for inclusion and choose not to participate.

**Baseline measurements**

Interested individuals are assessed at baseline within seven days of admission. First, they complete a questionnaire including information on pain, general health, occupation, education, physical and lifestyle factors, expectation to treatment outcome, and baseline values for the outcome measures.

Next, participants are examined using a standardized and previously validated study protocol [26]. The examination protocol consists of three parts:

1) A semi-structured interview including pain characteristics (frequency, duration, localization, provoking and relieving factors), symptoms from the lungs and gastrointestinal system, past medical history, height and weight, and risk factors for ischemic heart disease. Further, patients are classified into three types of chest pain: typical angina, atypical angina, or non-cardiac chest pain in accordance with Danish and international guidelines [19,21]. The patients are also classified into one of four classes of severity according to the criteria given by the Canadian Cardiovascular Society (CCS) [21,28]. Cardio-vascular performance is graded according to New York Heart Association (NYHA) [29].

2) A general health examination including blood pressure and pulse, heart and lung stethoscopy, abdominal palpation, neck auscultation, clinical signs of left ventricular failure, neurological examination of the upper and lower extremities in terms of reflexes, sensibility to touch, mus-
icle strength, and an orthopaedic examination of the neck and shoulder joints in order to rule out nerve root compression syndromes.

3) A specific manual examination of the muscles and joints of the neck, thoracic spine and thorax, including active range of motion, manual palpation for muscular tenderness on 14 points of the anterior chest wall, palpation for segmental paraspinal muscular tenderness, motion palpation for joint-play restriction of the thoracic spine (Th1–8), and end play restriction of the cervical and thoracic spine [26].

The examination program together with the detailed case history will be applied by a chiropractor to make a diagnosis of pain from the musculoskeletal system, CTA, according to the previously established criteria [26].

The timeline and overview of data collection is shown in Figure 1 (adapted from Perera et al. (2007)[30]). The timeline is shown vertically, and allocation of participants to study groups horizontally.

**MPS**

In order to evaluate the population in terms of ischemic heart disease all patients undergo MPS within two to four weeks following baseline evaluation. Using radionuclides the myocardial perfusion is evaluated to determine the presence of regional areas with decreased blood flow because of coronary artery disease. Detailed procedures for MPS are described in Appendix 1. MPS will also be used to compare and indirectly validate the musculoskeletal diagnosis.

**RCT**

All CTA positive patients (estimated 120 out of the initial 300 patients) will be included in the RCT. The aim of this part of the study is to establish the effectiveness of chiropractic treatment including spinal manipulation versus advice to promote self-management. Participants are only eligible for inclusion in the RCT if they are CTA positive and the examining clinician decides that manipulation might be the appropriate treatment. Patients for whom manipulation is thought not to be indicated will not be included in the RCT.

**Randomization**

The randomization sequence with a 1:1 allocation ratio has been computer generated by a researcher not involved in the project. Consecutively numbered sealed opaque envelopes containing the treatment allocation for each patient has been produced and eligible participants draw an envelope. The envelopes are arranged in blocks with varying block sizes. The examining clinician manages the hand over of the envelope to the participant, but is masked to the treatment allocation when determining eligibility to randomization.

**Treatments**

Participants will be randomized to receive one of two treatments: A course of chiropractic treatment including spinal manipulation (therapy group) or advice promoting self-management (advice group).

**Therapy group**

Participants in the therapy group will be assigned to a chiropractor in their local community. Participating chiropractors will have a university chiropractic degree and at least five years of clinical experience. Each chiropractor chooses an individual treatment strategy based on a combination of their findings, the patient history, and pragmatic, routine practice. The treatment will be modified to accommodate the age and physical condition of each patient. The treatment must, however, include high velocity, low amplitude manipulation directed towards the thoracic and/or cervical spine in combination with any of the following: Joint mobilisation, soft tissue techniques, stretching, stabilising or strengthening exercises, heat or cold treatment, and advice. The protocol specifies up to ten treatment sessions of approximately 20 minutes, 1–3 times per week for four weeks, or until the patient is pain free if this occurs within less than four weeks. The type of manipulation technique will not be standardized, and the treating chiropractor can manipulate the lumbar spine if he/she determines to do so. The chiropractors record the types of treatment rendered at all sessions.

**Advice group**

Advice is given in an approximately 15-minute session following the baseline assessment, and is directed towards promoting self-management. The participants are told that their chest pain generally has a benign, self-limiting course. The participants receive individual instructions regarding posture and two or three exercises aiming to increase spinal or muscle stretch based on clinical evaluation. They are advised to seek medical attention for re-evaluation (family physician, chest pain clinic or emergency department) in case of severe or unfamiliar chest pain. Further, the advice group is asked to refrain from seeking any manual treatment for the following four weeks.

**Outcome measures**

The outcomes are measures by self-report questionnaires that are collected at baseline, after four weeks (CTA positive patients only), and after three and 12 months (all patients) (see Figure 1).
Figure 1
Evaluation, intervention and follow up. (Adapted from Perera et al. 2007).

<table>
<thead>
<tr>
<th>Timeline</th>
<th>Participants</th>
<th>CTA negative</th>
<th>CTA positive (Therapy group)</th>
<th>CTA positive (Advice group)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (time = 0)</td>
<td>A B C D E</td>
<td>A B C D E</td>
<td>A B C D E</td>
<td>A B C D E</td>
</tr>
<tr>
<td>Determination of eligibility to RCT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Randomization</td>
<td></td>
<td></td>
<td>Not eligible for treatment</td>
<td></td>
</tr>
<tr>
<td>Initiation of treatment</td>
<td></td>
<td></td>
<td>Not eligible for treatment</td>
<td>F G</td>
</tr>
<tr>
<td>Approximately 2 weeks</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>4 weeks</td>
<td>B J K</td>
<td>B J K</td>
<td>B J K</td>
<td>B J K</td>
</tr>
<tr>
<td>12 weeks</td>
<td>B J</td>
<td>B J K</td>
<td>B J K</td>
<td>B J K</td>
</tr>
<tr>
<td>52 weeks</td>
<td>B J</td>
<td>B J K</td>
<td>B J K</td>
<td>B J K</td>
</tr>
</tbody>
</table>

**Symbol** | **Content**
---|---
A | Questionnaire completed by the patient including information on occupation, education, physical and lifestyle factors, and expectation to treatment outcome.
B | Questionnaire completed by the patient including information on pain intensity, general health and baseline values for the outcome measures.
C | Semi-structured interview, including pain characteristics, comorbidities, the past medical history, height and weight, and risk factors of ischemic heart disease.
D | General health examination, including blood pressure and pulse, stethoscopy, abdominal palpation, neck auscultation, clinical signs of left ventricular failure, neurological examination of the upper and lower extremities, and orthopaedic examination of the neck and shoulder joints.
E | Specific manual examination of the muscles and joints of the neck, thoracic spine and thorax, including active range of motion, manual palpation for muscular tenderness on the anterior and posterior chest wall, and motion palpation of the cervical and thoracic spine.
F | Therapy group. Chiropractic treatment consisting of high velocity, low amplitude manipulation directed towards the thoracic and/or cervical spine in combination with joint mobilisation, soft tissue techniques, stretching, stabilising or strengthening exercises, heat or cold treatment, and advice.
G | Advice group. Advice is given in an approximately 15 minute session following the baseline assessment, and is directed towards promoting self-management.
H | Myocardial Perfusion Scintigraphy
J | Global assessment. Improvement in chest pain and general health is rated by the participants using 7-point Likert-scales using the categories: Much worse, worse, a little worse, no change, a little better, better, and much better.
K | Health care costs/Cost-effectiveness analysis. Direct health care cost, direct non-health care costs and indirect costs are used in the economic evaluation as an indicator of cost-effectiveness.
Participants are asked to rate their worst level of chest pain during the last week, using an ordinal 11-point box scale (0 = no pain, 10 = the worst pain possible). Improvement in chest pain is rated by participants on a 7-point ordinal scale with responses ranging from "much worse" to "much better".

Secondary outcome measures

- Ordinal 11-point box scales (0 = no pain, 10 = the worst pain possible) will be used to rate chest pain "now" (i.e. on the day of examination/completion of questionnaire) together with the following types of pain over the last week: "worst" and "average" chest pain, "average" thoracic spine pain, "average" cervical spine pain, "average" shoulder and arm pain.

- Improvement in chest pain and general health is rated by the participants using an ordinal 7-point scale using the categories: "Much worse", "worse", "a little worse", "no change", "a little better", "better", and "much better".

- The general health status is measured by the Medical Outcomes Study Short Form 36-item Health Survey (SF-36) [31,32]. The SF-36 comprises 36 items that can be combined into eight multi-item summary scores: physical functioning, vitality, bodily pain, mental health, social functioning, role limitation due to physical health and due to emotional problems, and general health perception, plus one item assessing a change in health over the past year.

- The Patient Specific Functional Scale is developed to assess functional limitations in a variety of clinical presentations [33]. Participants will be asked to identify three important activities with which they are having difficulties or are unable to perform because of their problem. In addition to specifying the activities the participants will be asked to rate on an ordinal 11-point box scale the current level of difficulty associated with each activity.

- As a surrogate for the assessment of pain and quality of life, we will use the indicators "number of visits to family doctor", "number of hospitalizations", and "amount of prescribed drugs". The data will be obtained from the comprehensive national Danish central registers. Non-prescription medication use for chest pain is measured using self-report questionnaires at 12 and 52 weeks.

- Information about adverse events and side effects will be collected for the therapy group by the treating chiropractor before and after each treatment session.

Predictors of outcomes

- Prior to commencing treatment, patients are asked to rate their expectation towards treatment benefits on a 5-point scale, with responses ranging from "getting much worse" to "getting much better".

- The Brief Illness Perception Questionnaire (B-IPQ) assesses perception of illness by asking patients for their own belief about their condition [34]. The B-IPQ consists of eight items that can be combined into five cognitive components: Identity, cause, time-line, consequences and cure/control. These components together make up the patient’s perception of their illness. All eight items are measured using ordinal 11-point box scales.

Health care cost/Cost-effectiveness analysis

Direct health care cost, direct non-health care cost and indirect cost are used in the economic evaluation as an indicator of cost-effectiveness. Cost data are collected through patient self-report questionnaires at 12 and 52 weeks. Direct costs for each patient will represent the one-year aggregated chest pain related health care costs based on utilization and estimated costs. Health care utilization (within and outside the study) is measured using standardized clinician treatment forms (each chiropractic visit, weeks 1–4), and patient rated self-report questionnaires (baseline and weeks 12 and 52). Direct health care costs include costs related to study treatment, non-study health care health provider use, medication utilization, and hospitalizations for chest pain. Indirect costs of productivity loss is measured by patient self-report (weeks 12 and 52) using questions that measure lost or impacted work or activity days due to chest pain. The EuroQol 5D (modified version) [35,36], a multi-attribute, patient self-report utility scale measuring five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), is used as the cost-utility index. It is measured at baseline and weeks 4, 12, and 52.

Data analyses

Diagnostic study

All items of the examination protocol will be compared between CTA positive and CTA negative patients. In order to show the importance of any single variable in the decision making process the variables will be compared both within all included patients and in subgroups. Using the Classification and Regression Trees (CART) method [37] the decision making process will subsequently be reconstructed into a decision tree for predicting continuous dependent variables (regression) and categorical predictor variables (classification). The decision tree will be compared to the reconstructed decision process from the Christensen study comprising chronic chest pain patients [26]. The agreement between the old and the new decision tree will be analyzed. Further, the proportion of CTA
positive patients within the group of patients with normal MPS will be compared to proportion in the group of patients with abnormal MPS.

**Randomized controlled trial**

The size of the study sample was estimated using data from the study by Christensen et al. [27]. In this study, patients with suspected chronic stable angina pectoris were included. Improvement in chest pain over the last two weeks was assessed using an ordinal 5-point box scale. Using these results, a sample of 120 patients will provide 81% power to detect a shift in the distribution of the improvement in chest pain from 0%/5%/25%/45%/25% to 1%/10%/40%/40%/9%, which corresponds to the findings in the study by Christensen et al. The two studies are not similar in terms of patient characteristics (chronic versus acute chest pain), rating scales (5-point box scale versus 7-point box scale) or assessment period (two weeks versus one week). Nevertheless, a sample size of 120 patients was deemed sufficient.

The baseline scores of the patient demographics (e.g. age, gender, duration and history of complaints), primary and secondary outcomes will be used to compare the two intervention groups. Differences between baseline and follow up measurements will be calculated and compared. If necessary, adjustment for baseline variable will be made, using analysis of covariance (ANCOVA). A confirmatory, secondary analysis using the repeated measures, multivariate analysis of covariance (MANCOVA) will be used as an overall test for differences between groups. This will include both the primary and secondary patient-rated outcomes. The statistical analysis will be performed on the basis of the intention-to-treat principle, i.e. patients will be analysed in the treatment group to which they were randomly allocated. Finally, based on a prior definition of success, numbers needed to treat will be calculated. Outcomes of patient rated improvement will be dichotomized and success will be defined as patients rating "better" or "much better".

**Cost-effectiveness analysis**

A cost comparison of the therapy and advice group will be performed using data on direct and indirect costs. Cost differences between groups will be estimated using regression analysis where all chest pain-related costs in a year are regressed on treatment. A cost effectiveness analysis, using a mixed model linear regression analysis, will be conducted to compare the interventions, using patient-rated pain as the effective measure. Finally, a cost-utility analysis comparing the interventions will be performed using the EuroQol 5-D.

**Discussion**

This study is the result of a unique research collaboration between researchers with backgrounds in chiropractic, cardiology, nuclear medicine and biostatistics, and to our knowledge this is the first randomized clinical trial investigating the effect of manual treatment on chest pain of musculoskeletal origin.

The design of this study has been a challenging process since no standardized and validated outcome measures for chest pain of musculoskeletal origin exists. The study by Christensen et al. [27] formed the basis for the present study. However, methods and results from the Christensen study are not directly applicable in this study, mainly because of differences in the two populations in terms of pain duration and other characteristics. Patients with chronic chest pain often have repeated pain episodes of a relatively mild character, sometimes described as "discomfort" [21]. They may experience pain that is brought on in familiar situations and at an expected work load. This is in contrast to patients with acute chest pain, who often experience a very dramatic and intense pain episode, some for the first time, and the pain evokes considerable anxiety and fear of cardiac conditions. In order to adapt to the differences in populations, a pilot study comprising 36 patients was conducted to determine the population size, inclusion and exclusion criteria, questionnaires, logistics and the primary outcome measures in the RCT. Following this, the semi-structured interview and pain rating scales were adjusted.

**Diagnostic part**

An important part of the diagnostic procedure in this study is founded on manual examination of the muscles and joints. Palpation used as a diagnostic tool for spinal dysfunction has been subjected to criticism because of poor reproducibility and validity [38]. One of the major problems with the validation of palpation is that there is no golden standard to directly validate the findings. In the present study, this problem is addressed by using MPS as a by proxy measure to indirectly validate the CTA diagnosis. This is based on the hypothesis that in this population, patients who are CTA positive most likely will have fewer abnormal MPS than CTA negative patients. Data from the pilot study suggest that approximately 40% are CTA-positive, 15% have abnormal MPS, and 7% have both abnormal MPS and are CTA positive.

**Outcome measures**

We have chosen global perceived effect as one out of two primary outcome measures even though critique has been posted on the reliability and validity of global rating scales [39]. Global rating scales are typically correlated with the patients' present status and are not an unbiased measure of change. However, global rating scales are regarded as
clinically relevant and valid, and responsive to measure patients' perceived recovery. The global rating scale was also chosen, because during the pilot study we found that pain intensity levels were relatively low compared to for instance patients seeking care for low back pain. Patients initially reported very high levels of pain which then spontaneous decline in intensity within a very short period of time (hours to days), rendering pain a less than optimal primary outcome measure. Finally, we found that the Patient Specific Functional Scale [33] would not make a good primary outcome measure because many patients experience a first time episode of chest pain and, thus, do not feel limited in their daily activities.

**Interventions**

Chiropractic therapy may be an effective treatment for patients with acute chest pain, but this has only been investigated in one non-randomized trial [27]. A pragmatic approach was chosen for the therapy group. The exact content of chiropractic therapy may not be clear, and the potential active "ingredient" can not be known even after this trial is completed. The advantage of the pragmatic strategy is that if this trial provides evidence in favor of chiropractic therapy, the results can easily be implemented, but future trials will be needed in order to identify the specific components. Also, our design is not well suited to correct for attention bias. Advice was chosen as intervention for the second group, because it is intended to mimic usual care and will act as a control treatment. Chiropractors are an integrate part of the Danish primary health care system with approximately 15% of Danes consulting a chiropractor each year [40]. Patients that previously have received chiropractic treatment very often have specific expectation about what chiropractic treatment consists of. This means that choosing a sham or placebo treatment was not feasible in Denmark due to lack of naive patients, and because masking of patients to a sham or placebo treatment would not be possible.

In this study we have focused on two conditions that may cause episodes of chest pain, i.e. ischemic heart disease and CTA. Many other conditions may be present in these patients that could cause chest pain. Optimally, a thorough follow up, including evaluation of esophageal-gastro-intestinal conditions, would have been preferable to potentially diagnose some of the CTA-negative patients, but due to limitations in funding and time restraints such evaluation has not been possible.

In summary, this article presents the rationale and design of a multi-purpose study consisting of a prospective diagnostic study, and an RCT, with a cost-effectiveness study alongside the central trial. It is anticipated to be completed in 2008, at which time the results will be made available. The first part of this study may potentially demonstrate that a chiropractor is able to identify a subset of patients suffering from chest pain predominantly of musculoskeletal origin among patients dismissed from an acute chest pain clinic with no apparent cardiac condition. The long term goal is to establish whether manual palpation may be used as a part of the clinical examination to screen patients allowing for improvement in referral patterns. Furthermore knowledge about the benefits of manual treatment in patients with musculoskeletal chest pain will inform clinical decision and policy development in relation to clinical practice.

**Competing interests**

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

**Authors' contributions**

MJS is the study manager and was involved in the design of the study, secured funding for the study, wrote the firsts draft of the manuscript and participated in subsequent revisions. HWC participated in the design of the study, in particular with respect to the design of the physical examination protocol, and commented on the manuscript. JH participated in the design of the study, in particular with respect to the design of questionnaires and outcome measures, and commented on the manuscript drafts. WV participated in the design, especially regarding data analysis, and commented on the manuscript. PFHC and TH both participated in the design of the study, in particular with respect to the cardiologic and nuclear medicine aspects of this study, and commented on the manuscript. All authors read and approved the final manuscript.

**Appendix 1**

**Myocardial Perfusion Scintigraphy (MPS)**

All patients undergo an electrocardiographically gated rest MPS according to the rest part of a two-day protocol without attenuation correction [41]. $^{99m}$Tc-sestamibi (10 MBq, kg$^{-1}$, maximum 1100 MBq) is given 20 min. after sublingual administration of 0.5 mg nitro-glycerine followed 30–60 min. later by imaging using a dual-head gamma camera. A semi-automatic quantitative interpretation of perfusion and functional data is carried out using standard processing software (Auto QUAN'T 5.0.0) [42]. Abnormal segmental perfusion scores is computed in a 20-segment model using a 5-point perfusion scoring scale (0 = normal, 1 = equivocal, 2 = moderate, 3 = severe reduction of radioactivity, and 4 = absence of detectable tracer uptake in a segment based on a normal databases set up for each sex). The summed rest score (SRS) is obtained by adding the scores of each segment in the 20-segment model [43]. A study is judged abnormal if the sum of stress scores is = 4 with at least one segment having a score = 2. In case of an abnormal MPS at rest, additional stress imaging is carried out at least two days later using adeno-
The diagnostic accuracy of the MPS method has been reported elsewhere, and the estimated sensitivity and specificity for detecting significant coronary disease is 75% (95% CI 66%–82%) and 79% (95% CI 73%–84%), respectively [44].

Acknowledgements
The study is funded by the Nordic Institute of Chiropractic and Clinical Biomechanics, the County of Funen, and the Foundation for Chiropractic Research and Postgraduate Education.

References

Pre-publication history
The pre-publication history for this paper can be accessed here:

http://www.biomedcentral.com/1471-2474/9/40/prepub
B. Paper II
Non-cardiac chest pain in patients admitted to an emergency cardiology department.

Mette Jensen Stochkendahl, MSc\textsuperscript{1,2}; Henrik Wulff Christensen, DC, MD, PhD\textsuperscript{2}; Jan Hartvigsen, DC, PhD\textsuperscript{1,2}; Poul Flemming Høilund-Carlsen, MD, DMSci\textsuperscript{3}; Torben Haghfelt, MD, DMSci\textsuperscript{4}.

1. Institute of Sports Science and Clinical Biomechanics, University of Southern Denmark, Part of Clinical Locomotion Science.
3. Department of Nuclear Medicine, Odense University.
4. Department of Cardiology, Odense University Hospital.

ABSTRACT

Objectives: To describe the prevalence of recorded chest pain and clinical characteristics in patients admitted to an emergency cardiology department with suspected acute coronary syndrome (ACS), and compare characteristics of patients with and without ischemic heart disease (IHD).

Methods and Results: In total, 758 consecutive patients were identified. Clinical characteristics and diagnoses were extracted from medical files of 420 sufferers of chest pain. Sixteen percent had ACS. In patients without ACS, only 47\% were given a definitive diagnosis, angina pectoris (AP) being the most frequent (30\%). In all subgroups, recurrent pain episodes (43-58\%) and readmissions to hospital (37-56\%) were frequent. Pain characteristics and risk factors of IHD were not significantly different in patients with and without ACS. However, differences in risk factors of IHD were observed, but data were too few and unsystematic to allow further analysis.

Conclusion: In patients with suspected, but not proven, ACS, a high proportion suffered from non-cardiac chest pain. However, available data did not allow for clinically useful differentiation of subgroups. Structured interviews and more systematic recording of findings may be a way of preventing unnecessary admissions and expedite exclusion of cardiac disease and early discharge.
INTRODUCTION

In the United States, acute chest pain is the second most common cause of visits to emergency departments accounting for five per cent or more than five million visits each year.\(^1\) In Denmark with its 5.4 million inhabitants, acute chest pain is one of the most common reasons for hospital admission; in 2004 more than 48,000 admissions for ischemic heart disease (IHD) were registered.\(^2\) The prevalence and nature of chest pain in patients admitted to an emergency cardiology department are, however, relatively unknown.\(^3\) A sizeable minority of patients in whom an acute cardiac condition is excluded is categorized as having “non-cardiac” chest pain and discharged without a diagnosis or a plan for follow-up.\(^4\)\(^-\)\(^6\) These patients frequently experience persistent or recurrent symptoms resulting in depression, anxiety and a decrease in daily activity,\(^7\) reactions often ascribed to the absence of reassurance that the symptoms do not indicate life-threatening disease.\(^5\)\(^;\)\(^8\) Moreover, the lack of a diagnosis may cause additional investigation with further anxiety and time lost from work.\(^5\)

The natural history and characteristics of patients with this kind of non-cardiac chest pain are rather unknown and the prognosis is not well established.\(^5\)\(^;\)\(^9\) With new biochemical markers of ACS and acute revascularisation procedures cardiology focus on patients with non-cardiac chest pain has diminished.\(^10\) Besides, the risk-factor profile of patients with ACS has changed: The frequency of smoking and levels of serum cholesterol have decreased, whereas the occurrence of overweight, non-insulin dependent diabetes mellitus, and the proportion of elderly have increased.\(^11\) Hospitals have observed a decline in the number of presentations with acute myocardial infarction and a proportionately greater increase in admissions of patients with stable and unstable angina and non-cardiac chest pain.\(^9\)\(^;\)\(^12\) These increases may have important financial implications and support the development of services to prevent unnecessary admissions.\(^13\) We described the prevalence of various types of chest pain and the clinical characteristics of patients admitted for suspected ACS. In patients discharged within 24 hours without a diagnosis of ACS (non-ACS), characteristics of patients with and without IHD were compared.

METHODS

**Design**

Cross-sectional, retrospective study using file data of consecutive patients admitted to a university hospital emergency cardiology department.

**Population**

From 1 May 2004 to 30 June 2004, all consecutive patients admitted to the hospital’s emergency cardiology unit serving about 300,000 inhabitants were identified. Patients admitted more than once were registered on each occasion. This unit receives patients admitted with chest pain under observation for ACS as well as patients with other acute cardiac related conditions that do not necessarily require an intensive care unit.
Diagnoses
At discharge, all patients were assigned one or more relevant diagnoses by the attendant cardiologist. The diagnosis of ACS was made on the basis of serial determinations of cardiac biochemical ischemic markers, i.e., creatine kinase MB (mass) and troponin T, and serial electrocardiograms using standard procedures following international guidelines.(14) In patients without ACS, the diagnosis was based on further clinical findings including observation, ultrasound, chest x-ray, and any serial physical examination deemed necessary. All diagnoses were given according to the International Classification of Disease (ICD), 10th revision.(15) In some patients, the definitive diagnosis was considered a ‘working diagnosis’ since additional testing might succeed, e.g., gastroscopy, lung scintigraphy, elective coronary angiography. The normal procedures of the department were followed in every case. Only results from procedures performed during admission were considered in this study.

Data extraction and variables
Medical records were reviewed by the principal investigator to identify all patients presenting with acute chest pain as their primary complaint. Using predefi ned checklists, data were extracted and the reason for admission classified as either chest pain, feeling of dysrhythmia, feeling of dyspnoea, or ‘other’. In patients classified as having chest pain, a full list of data was extracted including demographics, pain characteristics, risk factors for IHD, previous cardiac history, referral pattern, physical findings, electrocardiogram results, serial determinations of biochemical ischemic markers and findings from ultrasound, exercise test, and coronary angiography (if performed). Referral for any further testing after discharge and/or any treatment plans was also recorded.

All diagnoses at discharge were recorded and patients categorised into one of two groups according to the primary diagnosis: ACS (ICD codes: I200, I21-I219) or no ACS. If the primary diagnosis was insufficient to give a relevant explanation of the patient’s chest pain, the secondary diagnosis was taken into account. If categorisation was still not possible using the diagnostic codes, the patient medical records and examination findings were reviewed by the principal author and a professor in cardiology (TH), and a diagnosis was reached by consensus.

Patients without ACS were classified into subgroups following the same procedures. The subgroup with angina pectoris included patients with stable angina pectoris, previous myocardial infarction, chronic ischemic heart conditions and hypertension as primary diagnoses.

Statistics and analyses
For all variables, descriptive statistics were used to report frequency distributions. Pain characteristics were evaluated using univariate statistics for their association with the occurrence of a cardiac or non-cardiac diagnosis. These associations were calculated by logistic regression and expressed using odds ratios (OR’s) and 95% confidence intervals (CI’s). When applying the t-test, p < 0.05 (two-sided) was considered statistically significant. Analyses were performed using STATA (Stata Statistical Software: release 9.2. Stata Corp, College Station, TX, USA).
RESULTS

Prevalence
During the three months, 705 patients were admitted to the cardiology emergency department on 758 occasions. Of these, 661 (94%) were admitted once, while 38 (5%), 4 (0.6%), and 2 (0.3%) were admitted two, three, or four or more times, respectively. In the 705 patients, chest pain was the primary reason for admission on 420 (55%) occasions (Figure 1).

Patient characteristics
A total of 66 patients (16%) was diagnosed with ACS (Table I). The majority of both ACS and non-ACS patients were men, but female patients were relatively more frequent (39%) in the non-ACS than the ACS group (27%). Female patients were older than male patients (mean age 65.5 versus 59.6 years, p<0.01), and ACS-patients were older than non-ACS patients (mean age 66.4 versus 61.0, p<0.01).

Pain characteristics
Non-ACS patients were more likely to have previous episodes of chest pain, aggravated by deep breathing, and referred for additional testing (Table II). However, the majority of differences were not statistically significant, including items of pain descriptors, aggravating or relieving factors, duration and frequency of pain, or risk factors of IHD. As a whole, this kind of additional information was sparse or lacking in many patients, leaving limited and incomplete data for subgroup analysis (Table II).

Comparison of subgroups of patients without ACS
Based on ICD-10 codes, we identified eight subgroups of non-ACS patients (Table III). A definitive diagnosis was given in half of these patients, angina pectoris being the most frequent (30%). In 167 of 354 non-ACS patients (47%), no definitive diagnosis was given. Musculoskeletal or oesophago-gastro-intestinal disease was reported in only three percent of patients, respectively.

When compared to non-ACS patients with angina pectoris (Table II), non-ACS patients without angina were significantly less likely to have had previous episodes or admissions for chest pain, to report pain of less than three months duration, daily pain, during physical activities or rest, to have hypercholesterolemia or be former smokers. Not unexpected, with regard to conditions defining angina pectoris diagnosis, non-ACS patients without angina were much less likely to have hypertension, previous myocardial infarction or revascularisation procedures performed, whereas they were twice as likely to be referred for further testing. There was a tendency to increased likelihood of missing data in patients without angina pectoris.

Diagnostic procedures and results
Expected significant differences between ACS and non-ACS patients were found with regard to results of procedures defining the diagnosis of ACS (Table IV). Non-ACS patients were less likely to have elevated cardiac biomarkers or abnormal findings on the electrocardiogram or coronary
angiography, whereas other diagnostic procedures revealed no differences between groups. Note that several findings were in contradiction with the final diagnosis.

DISCUSSION

The majority (55%) of admitted patients had chest pain as their primary complaint, but at the same time the majority (84%) of these 55% did not have ACS. There was a high frequency of recurring chest pain in both ACS and non-ACS patients (32% and 50%, respectively), and almost 50% of all patients had had at least one previous admission to the emergency department (Table II).

Unfortunately, for both patient groups it was not possible to retrieve a comprehensive description of chest symptoms from their records. The type of chest pain given in official guidelines was not systematically recorded and characteristics like provoking or relieving factors, quality and duration of pain, and risk factors for IHD (Table II) were noted too seldom to allow meaningful comparisons. This lack of recorded characteristics that may differentiate patients with chest pain was also observed in an Austrian report,(16) whereas in a Swedish study based on patient interviews, distinct differences between subgroups of chest pain patients could be identified.(10) In the latter study, patients with non-cardiac chest pain reported more intense and continued pain provoked at both rest and during activity compared to patients with IHD, and patients with non-cardiac chest pain had more painful and more complex pain syndromes mimicking the pain seen in chronic pain syndromes.(10) This kind of information was hardly present in the files of our study, in which there was a tendency to focus on symptoms relating to specific cardiac conditions. Thus, the inability to detect differences was to a great extent caused by incomplete patient files or biased questioning. For our retrospective analysis, we selected characteristics recommended in recent guidelines and textbooks to make or exclude a diagnosis of IHD.(14;17) However, in a busy clinical routine, overemphasis may be put on questions relating to acute conditions at the expense of recording more detailed information needed for research purposes. Thus, a major advantage of the Swedish study was its use of research specific interviews compared to our retrospective data extraction.

In only three percent of patients, a musculoskeletal or a gastro-oesophageal disease was noted in the routine as potential source of angina. This corresponds only moderately with the literature reporting frequencies of 7-23% of musculoskeletal and about 5-15% of gastro-oesophageal conditions as potential sources in acute medical settings.(5;18-20) Further, in almost 50% of our patients without ACS, a definitive diagnosis was not established. There may be several reasons for this. One is that the department is reimbursed by the local county at a lower rate for a specific than for a non-specific cardiac diagnosis, because the latter implies more extensive testing and thus a higher reimbursement. Secondly, referral for further testing was recommended in about half of the patients without ACS with a significant higher proportion (57 %) in the subgroup without angina pectoris indicating that this category was more often given a ‘working diagnosis’. This may in part explain the high number of patients with a non-specific diagnosis and illustrates that when patients are categorised post hoc as having angina pectoris this often had to be done in the absence of an objective cause of cardiac chest pain.
In our survey, the diagnosis of angina pectoris was based on codes for previous and present conditions and episodes of chest pain, including angina pectoris, previous myocardial infarction, chronic ischemic heart conditions as well as hypertension. Therefore, the current episode of chest pain may sometimes reflect another underlying condition and, consequently, may have been misclassified. Our study was based on a single emergency cardiology department and, thus, do not necessarily reflect the routines and practices of other similar units, the routines of which may vary considerably inside and outside Europe.

We identified a high proportion (84%) of patients without ACS among sufferers of chest pain with a large proportion of readmissions to hospital (45%). These large categories of patients are poorly described in the literature in terms of pain characteristics and risk factors, just as they were in the reports of the present study. Nonetheless, further sub-classification of patients without ACS into relevant diagnoses was indeed possible, but the quality and sparseness of the recorded data is a caveat to improve routine procedures to secure more valid data for future clinical research on acute chest pain.
REFERENCES


Figure I. Patient flow chart - reasons for admission.

Emergency cardiology department
n=758

Not chest pain
n=338
(44.5%)

Chest pain and observation for ACS
n=420
(55.5%)

ACS
n=66
(15.7%)

No ACS
n=354
(84.3%)

ACS=Acute coronary syndrome
**Table I.** Age and gender of patients with chest pain.

<table>
<thead>
<tr>
<th>Patients characteristics</th>
<th>Chest pain, all n=420</th>
<th>Non-ACS n=354</th>
<th>ACS n=66</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>264 (62.9)</td>
<td>216 (81.8)</td>
<td>48 (18.2)</td>
<td></td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>156 (37.1)</td>
<td>138 (88.5)</td>
<td>18 (11.5)</td>
<td></td>
</tr>
<tr>
<td>Age (years)¹</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>61.8 ±15.6 [17; 96]</td>
<td>61.0 ±15.8 [17; 95]</td>
<td>66.4 ±13.5 [43; 96]</td>
<td>0.009</td>
</tr>
<tr>
<td>Women</td>
<td>65.5 ±15.4 [25; 95]</td>
<td>64.9 ±15.6 [25; 95]</td>
<td>70.1 ±13.2 [45; 88]</td>
<td>0.19</td>
</tr>
<tr>
<td>Men</td>
<td>59.6 ±15.3 [17; 96]</td>
<td>58.4 ±15.4 [17; 92]</td>
<td>65.1 ±13.5 [43; 96]</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Data for age are expressed as mean, standard deviations (±SD) and range [in square brackets].
Table II. Chest pain characteristics and risk factors for ischemic heart disease.

<table>
<thead>
<tr>
<th></th>
<th>Non-ACS (n=354)</th>
<th>ACS (n=66)</th>
<th>No angina pectoris (n = 247)</th>
<th>Angina pectoris (n= 107)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Frequency of pain</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous episodes of</td>
<td>177 (50.0)</td>
<td>21 (31.8)</td>
<td>2.14</td>
<td>104 (42.1)</td>
</tr>
<tr>
<td>chest pain</td>
<td></td>
<td></td>
<td></td>
<td>73 (68.2)</td>
</tr>
<tr>
<td>Duration of symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 3 months</td>
<td>70 (19.8)</td>
<td>10 (15.2)</td>
<td>1.38</td>
<td>40 (16.2)</td>
</tr>
<tr>
<td>3 – 12 months</td>
<td>18 (5.1)</td>
<td>2 (3.0)</td>
<td>1.71</td>
<td>11 (4.5)</td>
</tr>
<tr>
<td>&gt; 12 months</td>
<td>20 (5.7)</td>
<td>4 (6.1)</td>
<td>0.93</td>
<td>11 (4.5)</td>
</tr>
<tr>
<td>Missing</td>
<td>246 (69.5)</td>
<td>50 (75.8)</td>
<td>0.73</td>
<td>185 (74.9)</td>
</tr>
<tr>
<td>Previous admissions</td>
<td>177 (50.0)</td>
<td>21 (31.8)</td>
<td>2.14</td>
<td>104 (42.1)</td>
</tr>
<tr>
<td>for chest pain</td>
<td></td>
<td></td>
<td></td>
<td>73 (68.2)</td>
</tr>
<tr>
<td><strong>Frequency of symptoms</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weekly</td>
<td>20 (5.6)</td>
<td>5 (7.6)</td>
<td>0.73</td>
<td>11 (4.5)</td>
</tr>
<tr>
<td>Daily</td>
<td>20 (5.7)</td>
<td>4 (6.1)</td>
<td>0.53</td>
<td>6 (2.4)</td>
</tr>
<tr>
<td>Missing</td>
<td>314 (88.7)</td>
<td>57 (86.4)</td>
<td>1.24</td>
<td>230 (93.1)</td>
</tr>
<tr>
<td><strong>Word descriptors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crushing</td>
<td>167 (39.4)</td>
<td>26 (47.2)</td>
<td>1.37</td>
<td>114 (46.2)</td>
</tr>
<tr>
<td>Squeezing</td>
<td>36 (10.2)</td>
<td>6 (9.1)</td>
<td>1.12</td>
<td>22 (8.9)</td>
</tr>
<tr>
<td>Stabbing</td>
<td>25 (7.1)</td>
<td>3 (4.6)</td>
<td>0.74</td>
<td>22 (8.9)</td>
</tr>
<tr>
<td>Missing</td>
<td>122 (34.5)</td>
<td>32 (48.5)</td>
<td>0.65</td>
<td>95 (34.4)</td>
</tr>
<tr>
<td><strong>Aggravating factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical activity</td>
<td>90 (25.4)</td>
<td>15 (22.7)</td>
<td>1.16</td>
<td>46 (18.6)</td>
</tr>
<tr>
<td>Rest</td>
<td>85 (24.0)</td>
<td>15 (22.7)</td>
<td>1.07</td>
<td>51 (20.7)</td>
</tr>
<tr>
<td>During sleep</td>
<td>50 (14.1)</td>
<td>12 (18.2)</td>
<td>0.74</td>
<td>31 (12.6)</td>
</tr>
<tr>
<td>Movement of body</td>
<td>19 (5.4)</td>
<td>2 (3.0)</td>
<td>0.81</td>
<td>16 (6.5)</td>
</tr>
<tr>
<td>Deep breathing</td>
<td>52 (14.7)</td>
<td>3 (4.6)</td>
<td>0.04</td>
<td>11.1 [11.1; 16.83]</td>
</tr>
<tr>
<td>Missing</td>
<td>115 (32.5)</td>
<td>34 (51.5)</td>
<td>0.45</td>
<td>85 (34.4)</td>
</tr>
<tr>
<td><strong>Relieving factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nitroglycerine</td>
<td>95 (28.8)</td>
<td>23 (34.9)</td>
<td>0.69</td>
<td>59 (23.9)</td>
</tr>
<tr>
<td>Duration of single</td>
<td>19 (5.4)</td>
<td>1 (1.5)</td>
<td>3.69</td>
<td>14 (5.7)</td>
</tr>
<tr>
<td>episodes of pain</td>
<td>151 (42.7)</td>
<td>31 (47.0)</td>
<td>0.84</td>
<td>108 (43.7)</td>
</tr>
<tr>
<td>Timeline from debut</td>
<td>46 (13.0)</td>
<td>12 (18.2)</td>
<td>0.67</td>
<td>33 (13.4)</td>
</tr>
<tr>
<td>of pain to admission</td>
<td>138 (39.0)</td>
<td>20 (30.3)</td>
<td>1.47</td>
<td>90 (36.4)</td>
</tr>
<tr>
<td>&gt;3 hours</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drinking</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk factors of IHD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>99 (28.0)</td>
<td>17 (25.8)</td>
<td>1.12</td>
<td>47 (19.0)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>170 (48.0)</td>
<td>33 (50.0)</td>
<td>0.92</td>
<td>95 (38.5)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>41 (11.6)</td>
<td>9 (13.6)</td>
<td>0.83</td>
<td>24 (9.7)</td>
</tr>
<tr>
<td>Family history of IHD</td>
<td>221 (62.4)</td>
<td>45 (68.2)</td>
<td>0.78</td>
<td>164 (66.4)</td>
</tr>
<tr>
<td>Smoking</td>
<td>98 (27.9)</td>
<td>18 (27.3)</td>
<td>1.02</td>
<td>76 (30.8)</td>
</tr>
<tr>
<td>Never</td>
<td>137 (38.7)</td>
<td>25 (37.9)</td>
<td>1.03</td>
<td>97 (39.3)</td>
</tr>
<tr>
<td>Current</td>
<td>88 (24.9)</td>
<td>16 (24.2)</td>
<td>1.03</td>
<td>52 (21.1)</td>
</tr>
<tr>
<td>Pre-existing CAD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous AMI</td>
<td>78 (22.0)</td>
<td>12 (18.2)</td>
<td>1.27</td>
<td>40 (16.2)</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>45 (12.7)</td>
<td>5 (7.6)</td>
<td>1.78</td>
<td>14 (5.7)</td>
</tr>
<tr>
<td>Previous CAGB</td>
<td>51 (14.4)</td>
<td>8 (12.1)</td>
<td>1.22</td>
<td>25 (10.1)</td>
</tr>
<tr>
<td>Referred for further</td>
<td>183 (51.7)</td>
<td>22 (33.3)</td>
<td>2.14</td>
<td>141 (57.1)</td>
</tr>
<tr>
<td>testing</td>
<td></td>
<td></td>
<td></td>
<td>42 (39.3)</td>
</tr>
</tbody>
</table>

Note that characteristics with prevalence below 5%, e.g. pain described as sharp, or burning, pain provoked by sexual activity and in cold weather conditions are not included in this table.

IHD=Ischemic heart disease; CAD=Coronary artery disease; AMI=Acute myocardial infarction, PCI=Percutaneous coronary intervention, CABG=Coronary artery bypass grafting.
Table III. Subgroup classification of patients without ACS

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>n</th>
<th>(%)</th>
<th>ICD-10 codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-specific conditions</td>
<td>167</td>
<td>(47.2)</td>
<td></td>
</tr>
<tr>
<td>Factors influencing health status and contact with health services</td>
<td></td>
<td></td>
<td>all Z-codes</td>
</tr>
<tr>
<td>Mitral valve insufficiency and non-rheumatic aortic valve disorders</td>
<td></td>
<td></td>
<td>I340, I350,</td>
</tr>
<tr>
<td>Non-specific</td>
<td></td>
<td></td>
<td>I519, R060, R073, R079, R505, R559, T914, E669</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>107</td>
<td>(30.2)</td>
<td></td>
</tr>
<tr>
<td>Angina pectoris</td>
<td></td>
<td></td>
<td>I201, I208, I209, I251</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td>I119</td>
</tr>
<tr>
<td>Old myocardial infarction</td>
<td></td>
<td></td>
<td>I252</td>
</tr>
<tr>
<td>Chronic ischaemic heart disease</td>
<td></td>
<td></td>
<td>I259, I500, I501, I509</td>
</tr>
<tr>
<td>Dysrhythmia</td>
<td>17</td>
<td>(4.8)</td>
<td>I441, I471, I489, I498, R000, R001</td>
</tr>
<tr>
<td>Pulmonary conditions</td>
<td>19</td>
<td>(5.4)</td>
<td></td>
</tr>
<tr>
<td>Lunge infections</td>
<td></td>
<td></td>
<td>J10-J189, R091</td>
</tr>
<tr>
<td>Constrictive lung disease and abnormal findings on diagnostic imaging of lung</td>
<td></td>
<td></td>
<td>J459, R91</td>
</tr>
<tr>
<td>Lung emboli</td>
<td></td>
<td></td>
<td>I269</td>
</tr>
<tr>
<td>Peri-myocarditis</td>
<td>14</td>
<td>(4.0)</td>
<td></td>
</tr>
<tr>
<td>Pericarditis</td>
<td></td>
<td></td>
<td>I300 - I318B</td>
</tr>
<tr>
<td>Myocarditis</td>
<td></td>
<td></td>
<td>I409</td>
</tr>
<tr>
<td>Musculoskeletal disease</td>
<td>11</td>
<td>(3.1)</td>
<td>M549, M626</td>
</tr>
<tr>
<td>Oesophago-gastro-intestinal disease</td>
<td>10</td>
<td>(2.8)</td>
<td>K269 - K309, R108</td>
</tr>
<tr>
<td>Rheumatic heart disease</td>
<td>9</td>
<td>(2.5)</td>
<td>I109</td>
</tr>
</tbody>
</table>
Table IV. Numbers of diagnostic procedures reported and corresponding results.

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Non-ACS n=354</th>
<th>ACS n=66</th>
<th>n</th>
<th>mean ±SD</th>
<th>n</th>
<th>mean ±SD</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure</td>
<td>285</td>
<td>58</td>
<td>150.1 ± 27.5</td>
<td>142.6 ± 30.2</td>
<td>0.06</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>282</td>
<td>55</td>
<td>84.2 ± 15.2</td>
<td>82.2 ± 16.4</td>
<td>0.39</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart auscultation</td>
<td>348</td>
<td>63</td>
<td>63 (19.8)</td>
<td>11 (17.5)</td>
<td>1.17</td>
<td>[0.56; 2.62]</td>
<td></td>
</tr>
<tr>
<td>Abnormal</td>
<td>69</td>
<td>11</td>
<td>1 (0.3)</td>
<td>2 (0.3)</td>
<td>0.13</td>
<td>[0.07; 2.49]</td>
<td></td>
</tr>
<tr>
<td>Lung auscultation</td>
<td>346</td>
<td>63</td>
<td>63 (16.8)</td>
<td>15 (23.8)</td>
<td>0.64</td>
<td>[0.33; 1.33]</td>
<td></td>
</tr>
<tr>
<td>Abnormal</td>
<td>58</td>
<td>15</td>
<td>15 (4.3)</td>
<td>2 (3.1)</td>
<td>0.43</td>
<td>[0.18; 1.06]</td>
<td></td>
</tr>
<tr>
<td>Chest wall palpation</td>
<td>133</td>
<td>15</td>
<td>15 (4.3)</td>
<td>2 (3.1)</td>
<td>0.43</td>
<td>[0.18; 1.06]</td>
<td></td>
</tr>
<tr>
<td>Abnormal</td>
<td>70</td>
<td>6</td>
<td>6 (1.7)</td>
<td>1 (0.2)</td>
<td>0.12</td>
<td>[0.05; 0.30]</td>
<td></td>
</tr>
<tr>
<td>Electrocardiogram</td>
<td>351</td>
<td>66</td>
<td>66 (18.3)</td>
<td>41 (6.2)</td>
<td>10.78</td>
<td>[3.86; 41.56]</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>144</td>
<td>4</td>
<td>4 (1.1)</td>
<td>1 (0.2)</td>
<td>0.12</td>
<td>[0.05; 0.30]</td>
<td></td>
</tr>
<tr>
<td>ST-elevation AMI</td>
<td>5</td>
<td>27</td>
<td>27 (0.7)</td>
<td>40 (0.6)</td>
<td>0.021</td>
<td>[0.006; 0.06]</td>
<td></td>
</tr>
<tr>
<td>Non-elevation AMI</td>
<td>11</td>
<td>14</td>
<td>14 (0.4)</td>
<td>21 (0.3)</td>
<td>0.12</td>
<td>[0.05; 0.30]</td>
<td></td>
</tr>
<tr>
<td>Sign. ST-depression without AMI</td>
<td>8</td>
<td>0</td>
<td>0 (0.0)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Non-specific finding</td>
<td>183</td>
<td>21</td>
<td>21 (0.6)</td>
<td>31 (0.5)</td>
<td>1.33</td>
<td>[1.30; 4.30]</td>
<td></td>
</tr>
<tr>
<td>Cardiac ultrasound</td>
<td>200</td>
<td>41</td>
<td>41 (1.1)</td>
<td>63 (1.8)</td>
<td>0.43</td>
<td>[0.18; 1.06]</td>
<td></td>
</tr>
<tr>
<td>Abnormal</td>
<td>27</td>
<td>11</td>
<td>11 (0.3)</td>
<td>26 (0.4)</td>
<td>0.43</td>
<td>[0.18; 1.06]</td>
<td></td>
</tr>
<tr>
<td>Cardiac biomarkers</td>
<td>308</td>
<td>45</td>
<td>45 (1.2)</td>
<td>65 (1.0)</td>
<td>0.06</td>
<td>[0.002; 0.018]</td>
<td></td>
</tr>
<tr>
<td>Abnormal</td>
<td>11</td>
<td>39</td>
<td>39 (1.1)</td>
<td>86 (1.3)</td>
<td>0.06</td>
<td>[0.002; 0.018]</td>
<td></td>
</tr>
<tr>
<td>Coronary angiography</td>
<td>57</td>
<td>46</td>
<td>46 (1.3)</td>
<td>66 (1.7)</td>
<td>0.11</td>
<td>[0.027; 0.38]</td>
<td></td>
</tr>
<tr>
<td>Abnormal</td>
<td>31</td>
<td>42</td>
<td>42 (1.2)</td>
<td>91 (1.7)</td>
<td>0.11</td>
<td>[0.027; 0.38]</td>
<td></td>
</tr>
</tbody>
</table>
C. Paper III
Cervicothoracic angina identified by case history and palpation findings in patients with acute chest pain

Mette Jensen Stochkendahl, MSc¹,²; Werner Vach, PhD³; Jan Hartvigsen, DC, PhD¹,²; Poul Flemming. Hoilund-Carlsen, MD, DMScit; Torben Hagfelt, MD, DMScit; Henrik Wulff Christensen, DC, MD, PhD¹.

3. Clinical Epidemiology, Institute of Medical Biometry and Medical Informatics, University Medical Centre Freiburg, Germany.
4. Department of Nuclear Medicine, Odense University Hospital.
5. Department of Cardiology, Odense University Hospital.

ABSTRACT

Purpose: To investigate the decision-making process of a clinician in diagnosing musculoskeletal chest pain of cervicothoracic angina (CTA) in patients with acute chest pain of non-cardiac origin when supported by a structured protocol. Secondly, to investigate the performance of a previously suggested decision tree for patients with chest pain, followed by an investigation of the possibility of obtaining a corresponding decision tree for identification of CTA in acute chest pain and compare the two decision trees.

Methods: A prospective trial was performed at a university hospital. A total of 302 consecutive patients with an acute episode of chest pain of non-cardiac origin were assessed at baseline using self-report questionnaires, patient interview, general health examination and systematic palpation of the spine and chest wall to diagnose CTA. Using stepwise, recursive procedures for constructing decision trees, patient characteristics were associated with the CTA diagnosis and the decision-making process of the clinician reconstructed.

Results: Thirty eight percent of patients were diagnosed with CTA. The main determinants of the decision making process could be identified, and a decision tree was suggested.

Conclusion: The results of this study confirmed previous research indicating that clinicians used a combination of indicators, including systematic palpation of the spine and chest wall and items from the case history, to diagnose a musculoskeletal component in patients with acute chest pain. The main indicators for the diagnosis may be stable across different chest pain cohorts, but do not allow for uncritical adoption of complete classification schemes.
INTRODUCTION

Next to abdominal pain, chest pain is the most common reason that individuals visit an emergency department. In patients with chest pain, the first priority is to identify patients with acute coronary syndrome (ACS), and to identify other potentially life threatening disease. However, the differential diagnosis of chest pain is broad including pulmonary, musculoskeletal, gastrointestinal, psychiatric, and dermatological systems, and causes of undifferentiated chest pain may present diagnostic problems to clinicians.

As many as 20% of patients leave emergency departments without a diagnosis and a plausible explanation of their chest pain. Some of these patients continue to suffer from recurrent episodes of chest pain, and billions of dollars in medical expenditures and lost labor costs for this condition are incurred each year. Consequently, in order to provide appropriate explanations for patients’ symptoms and target treatment, developing methods to obtain definitive diagnoses in all patients with chest pain is important.

Decision trees and classification systems are such methods designed to assist clinicians in decision-making. In 2005, Christensen et al. reported on an examination protocol for screening patients with chest pain for musculoskeletal causes assessed in patients with suspected stable angina pectoris. Additionally, the authors introduced the term cervicothoracic angina (CTA) to define chest discomfort originating from the cervical spine or the thorax and suggested a decision tree (2005 decision tree) to serve as an example of how to base the diagnosis of CTA on an objective and reproducible procedure. The cornerstone of diagnosis encompassed systematic manual palpation of the neck, thoracic spine and chest wall in combination with a case history. As recommended for classification systems, the examination protocol was tested for reliability of single items and validated indirectly using myocardial perfusion scintigraphy.

Since patients with undifferentiated chest pain present in a variety of settings, it would be favorable if a decision tree for CTA could be used across these settings and in a variety of populations. Therefore, the objectives of this study were: 1) to investigate the decision-making process in diagnosing CTA in patients with acute chest pain of non-cardiac origin when supported by a structured protocol and to identify the most important determinants from the patient history and clinical examination; 2) to investigate the performance of the 2005 decision tree followed by 3) an investigation of the possibility of obtaining a corresponding decision tree for identification of CTA in acute chest pain and compare the two decision trees.

METHODS

Study population
We recruited consecutive patients discharged from an emergency cardiology department at an urban 1,000 bed university hospital. All patients were admitted because of an acute episode of chest pain suspected to be ACS and underwent the department’s standard evaluation program, including electrocardiogram and biochemical cardiac marker testing, to rule out ACS and any other obvious and significant cardiac or non-cardiac disease. After the patients were discharged, the study clinician (MJS) screened patient records to identify eligible participants who were then contacted
personally or by telephone, and invited to participate. A full list of inclusion and exclusion criteria is provided elsewhere. In short, those primary eligible were adults with an episode of acute chest pain, without ACS or other coronary artery disease or significant co-morbidity. This study was approved by the regional ethics committee and registered at www.clinicaltrials.gov, trial number NCT00373828.

**Baseline assessment**
After providing written, informed consent the participants were assessed at baseline by the study clinician using the study protocol proposed by Christensen et al. (Table 1).

**Data analysis**
To elucidate the decision-making process, we analyzed the association of each single variable of the protocol with the CTA diagnosis. For each of the five overall categories of palpation (i.e. anterior muscle tenderness, costosternal/xiphoid junction tenderness, paraspinal tenderness, joint-play restriction, and end-play restriction), we had, a priori, defined an indicator representing at least one positive finding in that category. To get a positive CTA diagnosis, the patient had to have biomechanical dysfunction, which is joint-play and/or end-play restriction of a degree that warrants spinal manipulation. In addition, we assumed that the clinician performed some form of conscious or subconscious preprocessing prior to her decision, and, therefore, we defined the following variables: 1) A summary score for each of the five parts of the palpation protocol; 2) for each palpation finding recorded separately for the left and the right side (paraspinal, anterior muscle, and costosternal junction tenderness), a binary variable ‘present on at least one side’; 3) a binary variable summarizing a finding in either anterior muscle tenderness or costosternal junction/xiphoid process tenderness; 4) the number of overall palpation findings, counting once anterior muscle tenderness and costosternal/xiphoid tenderness as two separate findings and once as one finding. The latter was done to facilitate comparison with the Christensen study, in which the two variables were collapsed into one indicator; and 5) body mass index. Additionally, we added mock indicators of CCS and type of angina by assigning the grade ‘0’ to those patients for whom CCS was not applied and ‘non-typical’ to those patients for whom type of angina was not applied. Overall, the protocol gave rise to 25 continuous, 70 ordinal, 28 categorical, and 232 binary variables to be considered.

To allow simple comparison, we changed ordinal and continuous variables to binary indicators before analyzing the association with the CTA status. For continuous and ordinal variables with more than 10 categories, we used four indicators defined by cut points corresponding to the 20, 40, 60 and 80 percentile. Otherwise, each category served as a cut point of its own. This way we ultimately considered 741 binary indicators.

First, in comparing the association of individual indicators with the CTA status, we evaluated pre-chosen indicators as suggested by Christensen et al. (i.e. palpation findings, presence, type and severity of angina, and presence of neck pain) or as suggested in textbooks and literature reviews from the field of cardiology. Next, we listed all indicators according to the lower boundary of the exact 95% confidence interval of the odds ratio (OR), thereby compromising between looking at effect estimates and p-values, and reported the top indicators allowing for
comparison with the pre-chosen indicators. Throughout the analyses and when presenting results, we defined the indicators so that they were positively associated with the CTA status (OR > 1.0). When describing the degree of association and the possible contribution to the decision process, we calculated the positive and negative predictive values. A high positive predictive value implied a condition that the clinician considered important for a CTA positive status, whereas a high negative predictive value implied a condition, for which absence was considered important for a CTA negative status.

When evaluating the performance of the 2005 decision tree, we evaluated the concordance between the CTA diagnosis assigned in this study and the suggested indicator(s) from the Christensen study using 2x2 tables and carried forward to the next step of the decision tree only unclassified patients.

When constructing a new CTA decision tree, we used the following recursive procedure in the tradition of constructing classification and regression trees: For all binary indicators, we computed the association with the CTA status, as described above. We removed all indicators with prevalence below 7.5% or above 92.5%, because they may give spurious signals, and sorted the remaining ones according to the lower boundary of the confidence interval of the ORs. Second, we inspected this list for indicators with a positive predictive value of at least 90% and tried to combine them into a simple rule to identify CTA positive patients. Then we applied the same principle for the negative predictive values to obtain a simple rule to identify CTA negative patients. Third, if both failed, we selected from the top indicators, checked their individual contribution by fitting a multiple logistic model and constructed a simple scoring rule defining a subgroup of patients with low scores and high negative predictive value and a subgroup with high scores and high positive predictive value. Note that in constructing the decision tree, we only considered indicators of palpation encompassing both sides in one variable (‘present on at least one side’). Analyses were performed using STATA (Stata Statistical Software, version 9.2. Stata Corp, College Station, TX, USA).

RESULTS
After screening of patient records, we found 458 patients eligible for baseline evaluation of which 309 consented to participation. Four patients were excluded after the baseline evaluation (two patients had mental illness, which made them unable to cooperate, one patient had received manual therapy in the days between admission and baseline assessment, and one patient was unable to read Danish), and, for three patients, questionnaires were lost resulting in 302 patients available for analysis.

Patient characteristics
Patient characteristics of the population are presented in Table 2. Participants who were predominantly male had a mean age of 52 years. For both SF36 summary component scales, participants had significantly lower scores compared with the scores in a reference population of healthy Danes aged 45-54 years indicating poorer health (PSC: 43.9 versus 50.4, p<0.01; MSC:
48.2 versus 54.1, p<0.01). Two thirds of patients reported previous episodes of chest pain, and except for diabetes, risk factors for IHD were present in approximately 1/3 of patients.

**Association of single variables with the CTA status**

Thirty eight percent of patients (n=115) had CTA. The pre-chosen indicators from the case history appeared with similar frequencies in the two groups (Table 3). Excepted was ‘sharp’ pain, which was about twice as likely in CTA positive patients, who were also more likely to report gradual onset of pain, debut not related to meals, pain provoked by movement of upper body, and pain relieved by pain killers.

With respect to the indicators suggested by Christensen et al., CTA positive patients were significantly more likely to have presence of palpation findings showing high negative predictive values (Table 4), whereas only a moderate association was seen for CCS classification of grade 0 and 1. We found only moderate, statistically non-significant associations for type of angina or presence of neck pain.

Table 5 presents the top 13 indications with the highest association to a CTA positive diagnosis representing the first three steps of the new decision tree (see below). Nine of the 13 indicators were elements of palpation with strong associations for a CTA positive status (ORs range: 3.43 - ∞), and high negative predictive values for most. Excepted was reproduction of pain by palpation of costa 4 or 5, which showed high positive predictive values of 0.86 and 0.75, respectively. Four indicators from the case history were present in the top 13, three of which were also present in the list of pre-chosen items (pain worse on movement of torso, pain relief on pain killers, pain debut not during a meal) (Table 3).

**The performance of the decision tree proposed by Christensen et al.**

Step I: In the first step of the 2005 decision tree, absence of joint-play restriction implied absence of CTA. In our data set, joint-play restriction was absent in 119 patients, but 23 were CTA positive (Table 4).

Step II: In the remaining 180 patients with joint-play restriction (for three patients no information was available), 2005 decision tree had type of angina as the next indicator declaring patients without typical or atypical angina CTA positive. However, we found no association between type of angina and CTA (Table 4): 45 were classified with typical or atypical angina of which 53% (n=24) were CTA positive, whereas 135 patients had non-cardiac chest pain or the definition could not be applied of which 48% (n=65) were CTA positive. As a result, in the 135 patients classified as CTA positive, 70 were false positives.

Step III: In the 45 patients with typical or atypical angina, the 2005 decision tree summed up a score based on the presence of three indicators, cervical spine pain, presence of four palpation findings and a CCS grade of one classifying patients with a score of zero or one CTA negative and patients with a score of three CTA positive. CCS was not classified in seven of the 45 patients, but if we include them as patients with low CCS, all three indicators were moderately associated with a positive CTA diagnosis (ORs: 2.58 for CCS, 1.56 for palpation findings, 1.82 for cervical spine pain). Eleven patients had a score of zero or one, but four were not classified
correctly, and 16 patients had a score of three, but five were misclassified. So in this step, we could classify 27 patients; 9 of them incorrectly.

Step IV: In the remaining 17 patients, a summary score based on the five indicators *end-play of Th4-Th5, end-play of Th5-Th6, joint-play Th5-Th6, sharp pain* and *pain relieved by rest* was suggested to classify a CTA positive diagnosis. However, in our population only two of these five indicators were positively associated with the CTA status: *end-play of Th4-Th5 and sharp pain*. Consequently, only two out of the nine patients were classified correctly.

To sum up the performance of the 2005 decision tree, 291 out of 302 patients (96%) were classified (the remaining were missed due to missing values or remained unclassified in step IV), of which 60.5% (n=176) were classified correctly.

### Reconstruction of the clinical decision-making process in patients with acute chest pain

Figure 1 shows the reconstructed decision tree and specifies all indicators and scores of each step of the decision tree. Table 5 shows accuracy statistics for indicators in step I-III.

**Step I:** As mentioned above, the presence of a biomechanical dysfunction is a condition *sine qua non* for a CTA positive status. Indeed in the analysis of all single variables, we observed that the presence of a biomechanical dysfunction had a negative predictive value of 100%. Thus in the first step, we declared all patients with absence of a biomechanical dysfunction CTA negative.

**Step II:** In the 232 remaining patients (CTA prevalence 48.3%), we found four indicators with a positive predictive value above 0.85: *Palpation of costa 3 and palpation of costa 4 reproduce pain*, and *palpation of pectoral minor or major tenderness/pain*. The two first and the two latter were highly correlated respectively, whereas there was no sign of an association across the two pairs. Correspondingly, we found 25 patients with both costae 3 and 4 findings or with both *pectoral minor and major muscles* findings and only one of them were CTA negative, i.e. this subgroup was associated with a positive predictive value of 0.96. In the same step, we found four indicators with a negative predictive value above 0.85: *muscular tenderness on anterior chest wall; 3 or more of the 5 palpation findings; anterior muscular tenderness or costosternal junction/xiphoid process tenderness; AP uncertain or negative*. The first three indicators were related by definition, whereas the last indicator showed no association to the other three. In the 30 patients with maximally two palpation findings and no anterior palpation indicators or with positive AP, only two were CTA positive, and this subgroup showed a negative predictive value of 0.93. Thus in the second step, we suggest to declare patients with both costa 3 and costa 4 palpation findings or with both pectoral major and minor muscle findings as CTA positive, and patients with maximally 2 of the 5 possible palpation findings and no tenderness/pain on anterior chest wall or with positive AP status as CTA negative (Rule I).

**Step III:** In the remaining 177 patients (CTA prevalence 48.6%), we failed to define subgroups with predictive values above 0.90, but found indicators with predictive values above 0.80. A multiple logistic regression model used on the top nine indicators, assigned odds ratios of similar size to all nine, and therefore, we constructed a simple summary score (Score I). In the 29 subjects with a score below or equal to two, only three were CTA positive, and in the 38 subjects with a score above or equal to six, only four were CTA negative corresponding to a negative
predictive value of 90% and a positive predictive value of 89%. As a result, we assigned patients in the first subgroup a CTA negative status and patients in the second subgroup a CTA positive status.

Step IV: In the remaining 110 patients (CTA prevalence 44.5%), the top ten indicators were identified. In a multiple logistic model, two indicators (male and not limited or slightly limited in walking up a set of stairs) were assigned odds ratios close to one, whereas all other indicators were assigned odds ratios above 3.0 of comparable magnitude leading to use a simple summary score using the remaining eight indicators (Score II). In the 44 patients with a score below or equal to four, we found only four CTA positive patients corresponding to a negative predictive value of 91%. In the 18 patients with a score of seven or eight, we found only one CTA negative patient corresponding to a positive predictive value of 94%. Hence, in the forth step we declared patients in the first subgroup CTA negative, patients in the second subgroup CTA positive, and patients with a score of five or six remained unclassified.

Step V: In the remaining 48 patients, we selected the top nine indicators. The multiple logistic regression assigned effects below zero to two indicators (moderate to extreme pain and at least one painful or two tender spots in anterior muscles), whereas all other effect estimates were of similar magnitude. Again, we used a simple summary score based on the remaining seven indicators (Score III). In the 12 patients with a score of zero or one, none were CTA positive, and in the 14 patients with a score higher or equal to four, none were CTA negative corresponding to predictive values of 100%. Only 22 patients remained unclassified.

DISCUSSION

Resume of findings
This study investigated the decision-making process of a clinician assessing patients with acute non-cardiac chest pain for CTA, in the present material 38%. The main determinants of the decision-making process consisted of overall palpation findings, numbers of palpation findings and indicators for absence of cardiac chest pain, which in combination formed the basis for a five-step classification tree. Using the top 13 indicators in step I-III of the decision tree with mainly high negative predictive values, resulted in classification of 64% of patients, of which 95% were classified correctly. The classification tree proposed by Christensen et al. resulted in moderately acceptable classification of patients, but comparable indicators of major importance were identified in both cohorts.

Association of single variables with CTA status
Typical chest pain qualities, such as pressure or aching pain, have traditionally been considered indicative of cardiac ischemia. However, formal investigations have demonstrated that these descriptors predicted acute myocardial infarction weakly or not at all. Although pressure-like pain was the most frequent type of pain in our study, the symptom had no discriminatory power consistent with the literature. CTA positive were more likely to report sharp pain, and these findings were supported by both the Christensen study and literature reviews, in which sharp pain significantly decreased likelihood of ACS. In the top 13 indicators of a CTA positive status,
we also found pain with gradual onset, provoked by movement of thorax, and relieved by pain killers. Pain provoked by movement was rarely found in the study by Christensen et al., but according to literature pain in positional change represents a non-ACS component.  

Palpation findings had high discriminating power and made up the top-7 most important indicators of a CTA positive status. In contrast to the Christensen study, findings on the anterior chest wall were more frequent. This is in line with the literature reviews stating that tenderness of the anterior chest wall decreases likelihood of ACS.  

Importantly, the majority of indicators of palpation and case history yielded high negative predictive values indicating that absence of the indicator implied a CTA negative diagnosis.

**The performance of the existing decision tree**

When applying the 2005 decision tree in the present population 96% of patients were classified, but only 60% correctly, thereby demonstrating the importance of testing generalizability prior to widespread implementation. In the first step of the decision tree, absence of joint-play restriction was defining of a CTA negative status. In the Christensen study, restricted joint-play was selected as the first indicator with the highest discriminatory power among the four overall palpation findings, whereas in our population, joint-play was the palpation indicator with the lowest association to CTA. This variation resulted in misclassification of 13% of patients.

In step two, 2005 decision tree had type of angina. In the present population, three quarters of the patients available in step two did not have stable angina. In the remaining patients only a non-significant difference between the 19 patients classified as typical (CTA positive prevalence of 37%) and the 26 patients classified as atypical (CTA positive prevalence of 65%) could be observed.

In step three and four, the performance of the 2005 decision tree suffered from the fact that the majority of indicators in the present population was only associated with a CTA positive diagnosis to a moderate degree.

Regardless of these shortcomings, 60% of the population were classified correctly when using the 2005 decision tree. To account for the difference frequency of type of angina, we conducted a post hoc analysis using the exact same procedure as described above, but omitting step 2. This modified approach resulted in classification of slightly fewer patients (n=266 patients, 88%), but with a slightly higher percentage classified correctly (n=207, 64%).

In summary, although we identified many of the same indicators highly associated with the CTA diagnosis in both studies, the 2005 decision tree failed to correctly identify patients at more than 60% accuracy. Major reasons were lower frequency of typical angina and the prevalence of certain palpation findings. However, we cannot exclude that the failure was caused partly by use of different criteria or weighting of criteria by the clinician in either study. In any case, this result corroborates that one should not uncritically use classification schemes across different cohorts.

**Reconstruction of the decision-making process**

Reconstructions of the decision-making process yielded that palpation findings combined with absence of indicators for cardiac chest pain, played a major role. Separation of CTA positive and
negative patients was achieved through combinations of several indicators to form simple scores, and by combining these we were able to nearly reconstruct the decision-making process. Overall, results of the two decision trees demonstrated that the main indicators for a CTA positive diagnosis may be stable across different populations, but caution should be taken before adopting complete classification systems.

Important criteria for a classification system are that it should be simple and easy to understand. From a first look, the decision tree for the acute patients does not appear very simple as it consists of many indicators. However, these indicators could be reduced to simple scores forming a ‘linear’ tree without ‘branches’ displaying a rather simple, hierarchical structure. In the top of the tree, number of palpation findings and major palpation findings combined with the absence of AP were the main indicators followed by more specific palpation findings and items from the case history. An additional criterion for a classification system is that it should be reproducible when used by different observers. The inter-observer reliability of overall CTA diagnosis was evaluated in a subset of the present cohort and results yielded substantial agreement between experienced observers.

Limitations
The most important limitation of the present study is the lack of a reference standard to compare the CTA diagnosis against. We have suggested a decision tree to facilitate the diagnosis, but the degree to which this diagnosis is actually correct is unknown. Indirect support for the validity of the CTA diagnosis may be found, if treatment targeted at structures believed to be pain generators, i.e. muscles and joints of the cervicothoracic spine and chest wall, results in positive response. We have identified several differences between the two suggested decision trees, but we cannot discriminate whether these differences were caused by clinician idiosyncrasies or differences in population characteristics. Our data did not apply to patients in primary sector settings whose symptoms may be different. Consequently, the discriminatory value of certain criteria could be different in a wider clinical setting including those types of patients we excluded. Moreover, we did not consider other potential causes of chest pain, and therefore could not allege CTA positivity to be the sole cause of pain.

Perspectives
Ultimately, classification systems are developed for identifying subgroups of patients to direct treatment and improve clinical efficiency and resource utilization. One potentially active treatment for CTA is spinal manipulation. To determine as to what degree patients can actually benefit from such treatment, the CTA positive patients of our study were included in a randomized controlled trial, the results of which shall be reported elsewhere.
CONCLUSION

The results of this study confirm previous research that, in the presence of information on palpation findings and case history in patients with chest pain, clinicians use a combination of several indicators when diagnosing CTA. The main indicators for a positive CTA status (overall palpation findings, number of palpation findings and absence of indicators for cardiac chest pain) as well as the type of minor indicators like pain provoking factors may be stable across different populations, but one should be cautious with adopting complete classification schemes.
REFERENCES


(22) Riddle DL. Classification and low back pain: a review of the literature and critical analysis of selected systems. Phys Ther 1998; 78(7):708-737.


**Figure 1.** The reconstructed decision tree.

The rhombs are showing variables defining subgroups. The rectangles show the values defining subgroups and the numbers of the CTA positive patients (left number) and the total number of patients (right number) in this subgroup. An arrow to the left means decision for a CTA-negative status, an arrow to the right means a decision for a CTA-positive status.

### Rule I
- Palpation of costa 3 or costa 4 reproduces pain
- Palpation of pectoral minor or major tender/painful
- 2 or less of the 5 palpation findings
- No tenderness on anterior muscular or costosternal/xiphoid junctions
- Angina pectoris positive

<table>
<thead>
<tr>
<th>Score I</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 or less</td>
</tr>
<tr>
<td>3-5</td>
</tr>
<tr>
<td>6 or more</td>
</tr>
</tbody>
</table>

### Score II
- Height > 170 cm
- No previous history of lung disease
- Previous episodes of chest pain
- No asthma
- Walking up a set up stairs, not at all limited to limited (SF36)
- Paraspinal tenderness at Th1
- Pain does not influence working abilities (SF36)
- Abdominal palpation normal
- Weight > 96 kg

<table>
<thead>
<tr>
<th>Score III</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 or less</td>
</tr>
<tr>
<td>2 or3</td>
</tr>
<tr>
<td>4 or more</td>
</tr>
</tbody>
</table>

### Score III
- Normal active cervical ROM
- Problems with doing usual activities (Euroqol)
- Dynamic dysfunction of Th3/4
- Shoulder/arm pain ≥ 5
- Duration of pain < 12 months
- ≥ 1 static palpation finding
- Moderate to extreme pain (Euroqol)
- > 1 painful or > 2 tender spots in anterior muscles
- Patient’s perception that pain originates in joints & muscles
Table 1. Baseline assessment of patients according to the examination protocol described by Christensen et al.\textsuperscript{10}

<table>
<thead>
<tr>
<th>Self-report questionnaire</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Pain intensity of chest, neck, thoracic and shoulder-arm pain, using numeric rating scales (range 0-10)</td>
</tr>
<tr>
<td>- General health (Medical Outcomes Study Short Form 36-item Health Survey (SF36))\textsuperscript{25,26} \textit{and} The EuroQol 5D (modified version))\textsuperscript{27}</td>
</tr>
<tr>
<td>- Occupation and education</td>
</tr>
<tr>
<td>- Physical and lifestyle factors</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Semi-structured interview</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Patient’s subjective feeling of pain (onset, frequency, duration, localization, provoking and relieving factors)</td>
</tr>
<tr>
<td>- Present and past episodes of chest pain</td>
</tr>
<tr>
<td>- Symptoms from the lungs and gastrointestinal system</td>
</tr>
<tr>
<td>- Past medical history</td>
</tr>
<tr>
<td>- Height and weight</td>
</tr>
<tr>
<td>- Risk factors for ischemic heart disease (family history of ischemic heart disease, smoking, blood cholesterol, hypertension, diabetes)</td>
</tr>
<tr>
<td>- Classification of angina*</td>
</tr>
<tr>
<td>- Type of angina (Danish and international guidelines)\textsuperscript{28,29}</td>
</tr>
<tr>
<td>- Severity of angina (Canadian Cardiovascular Society (CCS))\textsuperscript{30}</td>
</tr>
<tr>
<td>- Cardio-vascular performance (New York Heart Association).\textsuperscript{31}</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>General health examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Blood pressure</td>
</tr>
<tr>
<td>- Heart rate</td>
</tr>
<tr>
<td>- Heart and lung stethoscopy</td>
</tr>
<tr>
<td>- Abdominal palpation</td>
</tr>
<tr>
<td>- Neck auscultation</td>
</tr>
<tr>
<td>- Clinical signs of left ventricular failure noted</td>
</tr>
<tr>
<td>- Neurological examination of the upper and lower extremities (sensibility to touch and pain, reflexes and muscle strength)</td>
</tr>
<tr>
<td>- Orthopedic examination of the neck and shoulders to rule out nerve root compression syndromes.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Manual examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Sitting motion palpation of end play restriction in lateral flexion and rotation segmentally of the cervical and thoracic spine (C4-C7 and Th1-Th8).</td>
</tr>
<tr>
<td>- Prone motion palpation for joint-play restriction segmentally of the thoracic spine (Th1-Th8).</td>
</tr>
<tr>
<td>- Prone evaluation of paraspinal tenderness segmentally of the thoracic spine (Th1-Th8).</td>
</tr>
<tr>
<td>- Supine manual palpation of muscular tenderness of 14 points on the anterior chest wall.</td>
</tr>
<tr>
<td>- Supine evaluation of tenderness of the costo-sternal junctions of costa 2-6 and xiphoid process.</td>
</tr>
</tbody>
</table>

* Classification according to type of angina and CCS was only applied in patients with repeated episodes during the last four weeks.
Table 2. Patient characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 302</td>
</tr>
<tr>
<td>Age, years ±SD</td>
<td>52.5 ± 11.0</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>132 (43.7)</td>
</tr>
<tr>
<td>Weight, kg ±SD</td>
<td>82.3 ± 16.0</td>
</tr>
<tr>
<td>Height, cm ±SD</td>
<td>173.4 ± 10.0</td>
</tr>
<tr>
<td>Body Mass Index, kg/m² ±SD</td>
<td>27.3 ± 4.4</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg ±SD</td>
<td>137.7 ± 17.2</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg ±SD</td>
<td>87.7 ± 9.7</td>
</tr>
<tr>
<td>SF36</td>
<td></td>
</tr>
<tr>
<td>Physical health component scale ±SD</td>
<td>43.9 ± 8.8</td>
</tr>
<tr>
<td>Mental health component scale ±SD</td>
<td>48.2 ± 10.7</td>
</tr>
<tr>
<td>Previous episodes of chest pain, n (%)</td>
<td>196 (64.9)</td>
</tr>
<tr>
<td>Risk factors of ischemic heart disease*</td>
<td></td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>84 (28.4)</td>
</tr>
<tr>
<td>Hypercholesterolemia, n (%)</td>
<td>95 (31.5)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>99 (32.8)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>14 (4.7)</td>
</tr>
<tr>
<td>Engaging in daily light exercise, n (%)</td>
<td>136 (52.3)</td>
</tr>
<tr>
<td>Engaging in daily heavy exercise, n (%)</td>
<td>32 (23.9)</td>
</tr>
<tr>
<td>Married/living with someone, n (%)</td>
<td>249 (83.3)</td>
</tr>
<tr>
<td>Working, n (%)</td>
<td>196 (65.8)</td>
</tr>
<tr>
<td>College graduate, n (%)</td>
<td>68 (23.0)</td>
</tr>
</tbody>
</table>

Data are expressed as mean and standard deviations (±SD) or absolute numbers and relative frequencies (in parentheses).

* The risk factors were identified from the case history. In hypercholesterolemia, hypertension and diabetes information was based on whether the patient was in medical treatment or the condition had previously been diagnosed according to the patient.
Table 3. Accuracy statistics for pre-chosen specific items from the case history suggested in textbooks of cardiology associated with a CTA positive diagnosis in the entire population (n=302).

<table>
<thead>
<tr>
<th>CTA pos.</th>
<th>CTA neg.</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=112</td>
<td>n=190</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>How would you describe your symptoms?</strong></td>
<td></td>
</tr>
<tr>
<td>Not squeezing/pressure-like</td>
<td>32 (28.6)</td>
</tr>
<tr>
<td>Sharp</td>
<td>40 (35.7)</td>
</tr>
<tr>
<td>Not well demarcated</td>
<td>109 (97.3)</td>
</tr>
<tr>
<td>Diffuse</td>
<td>3 (2.7)</td>
</tr>
<tr>
<td>Burning</td>
<td>7 (6.3)</td>
</tr>
<tr>
<td>Not prickly</td>
<td>106 (94.6)</td>
</tr>
<tr>
<td>Other</td>
<td>32 (45.1)</td>
</tr>
<tr>
<td><strong>How did the pain start?</strong></td>
<td></td>
</tr>
<tr>
<td>Gradually</td>
<td>34 (30.4)</td>
</tr>
<tr>
<td>During physical activity</td>
<td>19 (17.0)</td>
</tr>
<tr>
<td>During psychic stress</td>
<td>14 (12.5)</td>
</tr>
<tr>
<td>With movement of torso</td>
<td>13 (11.6)</td>
</tr>
<tr>
<td>Not at rest</td>
<td>79 (70.5)</td>
</tr>
<tr>
<td>Not at sleep</td>
<td>101 (90.2)</td>
</tr>
<tr>
<td>Not during a meal</td>
<td>109 (97.3)</td>
</tr>
<tr>
<td>In cold weather</td>
<td>2 (1.8)</td>
</tr>
<tr>
<td><strong>Have you had previous episodes of chest pain?</strong></td>
<td></td>
</tr>
<tr>
<td>Less than 10 min</td>
<td>30 (38.0)</td>
</tr>
<tr>
<td>Not less than 1 h</td>
<td>12 (15.2)</td>
</tr>
<tr>
<td>More than 1 h</td>
<td>37 (46.8)</td>
</tr>
<tr>
<td><strong>How often do you have episodes?</strong></td>
<td></td>
</tr>
<tr>
<td>Monthly</td>
<td>34 (45.3)</td>
</tr>
<tr>
<td>Weekly</td>
<td>37 (49.3)</td>
</tr>
<tr>
<td>Not daily</td>
<td>22 (29.3)</td>
</tr>
<tr>
<td><strong>Symptoms for how long time?</strong></td>
<td></td>
</tr>
<tr>
<td>&lt; 3 mo</td>
<td>18 (23.4)</td>
</tr>
<tr>
<td>&lt; 12 mo</td>
<td>39 (50.7)</td>
</tr>
<tr>
<td><strong>Provoking factors?</strong></td>
<td></td>
</tr>
<tr>
<td>Physical activity</td>
<td>37 (32.1)</td>
</tr>
<tr>
<td>Movement of thorax</td>
<td>32 (28.6)</td>
</tr>
<tr>
<td>Rest</td>
<td>32 (28.6)</td>
</tr>
<tr>
<td>Not sleep</td>
<td>104 (92.8)</td>
</tr>
<tr>
<td>Leaning forward</td>
<td>7 (6.3)</td>
</tr>
<tr>
<td>Swallowing</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Deep breath</td>
<td>9 (8.0)</td>
</tr>
<tr>
<td>Not related to eating</td>
<td>109 (97.3)</td>
</tr>
<tr>
<td>Psychic stress</td>
<td>15 (13.4)</td>
</tr>
<tr>
<td><strong>Relieving factors?</strong></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>43 (38.4)</td>
</tr>
<tr>
<td>Movement of thorax</td>
<td>6 (5.4)</td>
</tr>
<tr>
<td>No effect of nitroglycerin</td>
<td>105 (93.7)</td>
</tr>
<tr>
<td>Pain killers</td>
<td>25 (22.3)</td>
</tr>
</tbody>
</table>
Table 4. Accuracy statistics for pre-chosen indicators of CTA as suggested by Christensen et al.\textsuperscript{10} associated with a CTA positive diagnosis in the entire population (n=302).

<table>
<thead>
<tr>
<th></th>
<th>CTA pos. n=112</th>
<th>CTA neg. n=190</th>
<th>Pos. predictive value</th>
<th>Neg. predictive value</th>
<th>OR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palpation*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior muscle tenderness</td>
<td>109 (97.3)</td>
<td>107 (56.3)</td>
<td>0.51</td>
<td>0.97</td>
<td>28.18 [8.80; 142.52]</td>
</tr>
<tr>
<td>Paraspinal tenderness</td>
<td>90 (80.4)</td>
<td>112 (59.3)</td>
<td>0.45</td>
<td>0.78</td>
<td>2.81 [1.58; 5.12]</td>
</tr>
<tr>
<td>End-play restriction</td>
<td>108 (96.4)</td>
<td>149 (79.3)</td>
<td>0.42</td>
<td>0.91</td>
<td>7.07 [2.43; 27.90]</td>
</tr>
<tr>
<td>Joint-play restriction</td>
<td>89 (79.5)</td>
<td>91 (48.7)</td>
<td>0.49</td>
<td>0.81</td>
<td>4.08 [2.31; 7.34]</td>
</tr>
<tr>
<td>Classification of angina</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type of angina\textsuperscript{†}, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not typical chest pain</td>
<td>7 (11.1)</td>
<td>23 (24.2)</td>
<td>0.44</td>
<td>0.77</td>
<td>2.56 [0.97; 7.53]</td>
</tr>
<tr>
<td>Non-cardiac chest pain</td>
<td>37 (58.7)</td>
<td>45 (47.4)</td>
<td>0.45</td>
<td>0.65</td>
<td>1.52 [0.76; 3.04]</td>
</tr>
<tr>
<td>CCS grade 0 or I\textsuperscript{‡}, n (%)</td>
<td>101 (92.7)</td>
<td>157 (83.9)</td>
<td>0.39</td>
<td>0.79</td>
<td>2.41 [1.03; 6.32]</td>
</tr>
<tr>
<td>Presence of neck pain</td>
<td>71 (64.0)</td>
<td>102 (54.0)</td>
<td>0.41</td>
<td>0.69</td>
<td>1.51 [0.91; 2.53]</td>
</tr>
</tbody>
</table>

* Number of patients with presence of palpation finding (yes/no) and relative frequencies (in parentheses).
† Classification of angina according to international and national Danish Guidelines.\textsuperscript{28,29}
‡ CCS=Classification of severity of chest pain according to the Canadian Cardiovascular Society.\textsuperscript{30}
Table 5. Accuracy statistics for step I-III individual indicator variables from the decision tree associated with a CTA positive diagnosis in the entire population (n=302).

<table>
<thead>
<tr>
<th>Indicator Variable</th>
<th>CTA pos. (<em>n</em>)</th>
<th>CTA neg. (<em>n</em>)</th>
<th>Pos. predictive value</th>
<th>Neg. predictive value</th>
<th>OR</th>
<th>[95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biomechanical dysfunction</td>
<td>112 (48.3)</td>
<td>120 (51.7)</td>
<td>0.48</td>
<td>1.00</td>
<td>=</td>
<td>[16.94; =]</td>
</tr>
<tr>
<td>3 or more of the 5 palpation findings</td>
<td>111 (99.1)</td>
<td>124 (65.3)</td>
<td>0.47</td>
<td>0.99</td>
<td>59.08</td>
<td>[9.80; 2388.9]</td>
</tr>
<tr>
<td>Muscular tenderness on anterior chest wall</td>
<td>109 (97.3)</td>
<td>107 (56.3)</td>
<td>0.51</td>
<td>0.97</td>
<td>28.18</td>
<td>[8.81; 142.52]</td>
</tr>
<tr>
<td>Palpation of costa 4 reproduces pain</td>
<td>36 (32.1)</td>
<td>3 (3.2)</td>
<td>0.86</td>
<td>0.71</td>
<td>14.53</td>
<td>[5.70; 43.15]</td>
</tr>
<tr>
<td>Anterior muscular tenderness or costosternal junctions/xiphoid process tenderness</td>
<td>110 (98.2)</td>
<td>134 (70.5)</td>
<td>0.45</td>
<td>0.97</td>
<td>22.99</td>
<td>[5.80; 197.43]</td>
</tr>
<tr>
<td>&gt; 1 painful or 2 tender spots on anterior muscles</td>
<td>93 (83.0)</td>
<td>76 (40.0)</td>
<td>0.55</td>
<td>0.86</td>
<td>7.34</td>
<td>[4.03; 13.74]</td>
</tr>
<tr>
<td>Costosternal junctions/xiphoid process tenderness</td>
<td>102 (91.1)</td>
<td>109 (57.4)</td>
<td>0.48</td>
<td>0.89</td>
<td>7.58</td>
<td>[3.64; 17.21]</td>
</tr>
<tr>
<td>Palpation of costa 5 reproduces pain</td>
<td>27 (24.1)</td>
<td>9 (4.7)</td>
<td>0.75</td>
<td>0.68</td>
<td>6.39</td>
<td>[2.75; 16.04]</td>
</tr>
<tr>
<td>Angina pectoris, uncertain or negative</td>
<td>109 (98.2)</td>
<td>155 (82.5)</td>
<td>0.41</td>
<td>0.94</td>
<td>11.60</td>
<td>[2.85; 101.30]</td>
</tr>
<tr>
<td>Intercostals muscle 5 tenderness or pain</td>
<td>68 (60.7)</td>
<td>59 (31.1)</td>
<td>0.54</td>
<td>0.75</td>
<td>3.43</td>
<td>[2.05; 5.76]</td>
</tr>
<tr>
<td>Pain worse on movement of torso</td>
<td>32 (28.6)</td>
<td>16 (8.4)</td>
<td>0.67</td>
<td>0.69</td>
<td>4.35</td>
<td>[2.16; 8.96]</td>
</tr>
<tr>
<td>Pain relief on pain medication</td>
<td>25 (22.3)</td>
<td>13 (6.8)</td>
<td>0.66</td>
<td>0.67</td>
<td>3.91</td>
<td>[1.82; 8.72]</td>
</tr>
<tr>
<td>Pain debut not during a meal</td>
<td>109 (97.3)</td>
<td>168 (88.4)</td>
<td>0.39</td>
<td>0.88</td>
<td>4.76</td>
<td>[1.37; 15.32]</td>
</tr>
</tbody>
</table>

Data are sorted by the lower boundary of the 95% confidence intervals [95% CI] of the odd ratios (OR).
D. Paper IV
Original Article

Examination of musculoskeletal chest pain – An inter-observer reliability study

Mads Hostrup Bruns, Mette Jensen Stochkendahl, Werner Vach, Alice Kongsted, Erik Poulsen, Jan Hartvigsen, Henrik Wulff Christensen

Institute of Sports Science and Clinical Biomechanics, University of Southern Denmark, Odense, Denmark
Nordic Institute of Chiropractic and Clinical Biomechanics, Part of Clinical Locomotion Science, Forskerparken 10A, Odense, Denmark
Department of Statistics, University of Southern Denmark, Odense, Denmark

ARTICLE INFO

Article history:
Received 30 June 2009
Received in revised form 23 September 2009
Accepted 7 October 2009

Keywords:
Reliability
Palpation procedure
Physical examination
Chest pain

ABSTRACT

Chest pain may be caused by joint and muscle dysfunction of the neck and thorax (termed musculoskeletal chest pain). The objectives of this study were (1) to determine inter-observer reliability of the diagnosis ‘musculoskeletal chest pain’ in patients with acute chest pain of non-cardiac origin using a standardized examination protocol, (2) to determine inter-observer reliability of single components of the protocol, and (3) to determine the effect of observer experience. Eighty patients were recruited from an emergency cardiology department. Patients were eligible if an obvious cardiac or non-cardiac diagnosis could not be established at the cardiology department. Four observers (two chiropractors and two chiropractic students) performed general health and manual examination of the spine and chest wall. Percentage agreement, Cohen’s Kappa and ICC were calculated for observer pairs (chiropractors and students) and all. Musculoskeletal chest pain was diagnosed in 45 percent of patients. Inter-observer kappa values were substantial for the chiropractors and overall (0.73 and 0.62, respectively), and moderate for the students (0.47). For single items of the protocol, the overall kappa ranged from 0.01 to 0.59. Provided adequate training of observers, the examination protocol can be used in carefully selected patients in clinical settings and should be included in pre- and post-graduate clinical training.

© 2009 Elsevier Ltd. All rights reserved.

1. Introduction

Chest pain is a symptom that can indicate a serious, life threatening condition, and it affects the daily life of numerous people. In the United States, chest pain results in 5% of all emergency department visits or approximately six million visits per year (McCaig and Nawar, 2006). However, less than half of these patients are diagnosed with a cardiac condition and over 50% are diagnosed with “non-cardiac” chest pain, which may relate to a range of disorders including musculoskeletal conditions (Capewell and McMurray, 2000).

Not surprisingly, patients with non-cardiac chest pain have a good prognosis for survival, but for many of these patients chest pain continues to present a problem (Nijher et al., 2001). Seventy five percent experience new episodes of pain, which in 20 percent leads to further contact with the health care system (Ockene et al., 1980; Launbjerg et al., 1997; Best, 1999). This is probably since the diagnosis of non-cardiac chest pain does not result in new treatment initiatives and as a result leaves the patients worried (Dart et al., 1983; McDonald et al., 1996). In order to clinically differentiate sub-groups of patients with non-cardiac chest pain and to optimize information and treatment plans, further diagnostic initiatives therefore appear warranted.

Practitioners of manual medicine, with status of primary health care provider, may encounter patients with chest pain. The professional responsibilities include proper assessment, documentation and appropriate and timely referral as needed. Systematic assessment of patients may be accomplished through use of classification systems or standardized evaluation protocols. Such systems have been tested in patients suffering from neck and low back pain, but have mainly been developed to identify sub-groups of patients with benign pain syndromes (Childs et al., 2004; Fritz et al., 2006; Cleland et al., 2007; Fritz and Brennan, 2007; Trudelle-Jackson et al., 2008). In a population study of low back pain, results indicate that palpation findings and single tests of mechanical dysfunction have limited clinical value in identifying patients with pain, whereas the collective use of several tests may increase diagnostic discrimination (Leboeuf-Yde and Kyvik, 2000).

Assessment and management of musculoskeletal chest pain, or even mid back pain, have largely been empirically based; however, in
Inclusion and exclusion criteria.

Table 1

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants included had to</td>
<td>Patients were not included if any of the following conditions were present</td>
</tr>
<tr>
<td>• Have chest pain as their primary complaint</td>
<td>• Acute coronary syndrome.</td>
</tr>
<tr>
<td>• Have an acute episode of pain of less than 7 days duration before admission.</td>
<td>• Previous percutaneous coronary intervention or coronary artery by-pass grafting.</td>
</tr>
<tr>
<td>• Consent to the standardized evaluation program at the cardiology department</td>
<td>• Chest pain from other definite cause, cardiac or non-cardiac. The condition must be verified clinically during admission (i.e. pulmonary embolism, pneumonia, dissection of the aorta, ...).</td>
</tr>
<tr>
<td>• Have pain in the thorax and/or neck.</td>
<td>• Inflammatory joint disease.</td>
</tr>
<tr>
<td>• Be able to read and understand Danish.</td>
<td>• Insulin dependent diabetes.</td>
</tr>
<tr>
<td>• Be between 18 and 75 year of age.</td>
<td>• Fibromyalgia.</td>
</tr>
<tr>
<td>• Be a resident of the Funen County, Denmark.</td>
<td>• Malignant disease.</td>
</tr>
<tr>
<td></td>
<td>• Apoplexy, dementia, or unable to cooperate.</td>
</tr>
<tr>
<td></td>
<td>• Major osseous anomaly.</td>
</tr>
<tr>
<td></td>
<td>• Osteoporosis.</td>
</tr>
<tr>
<td></td>
<td>• Pregnancy.</td>
</tr>
<tr>
<td></td>
<td>• Not willing to participate.</td>
</tr>
<tr>
<td></td>
<td>• Other.</td>
</tr>
</tbody>
</table>

2. Methods

2.1. Study population and recruitment

This study is part of a larger study addressing diagnosis and manual treatment of musculoskeletal chest pain. Inclusion and exclusion criteria are presented in Table 1 and have been described in detail elsewhere (Stochkendahl et al., 2008). In brief, for this part of the study, 80 patients were included from September 2007 to March 2008. Patients with non-specific chest pain were recruited from the emergency cardiology department at Odense University Hospital, Denmark. All patients had been admitted with suspected acute coronary syndrome. To identify chest pain patients with non-cardiac chest pain, one of the authors (MJJS) scanned the patient medical records for inclusion and exclusion criteria (Table 1).

Following discharge from the hospital, eligible patients were contacted, and written consent was obtained from those willing to participate. In case of doubt concerning eligibility of a patient, the medical record was presented to an experienced cardiologist and consensus was reached. The patients were examined in this study within two weeks following their episode of acute chest pain. Approval has been granted by the regional ethics committee for Funen and Vejle Counties, Denmark, approval number VF 20060002.

2.2. Observers and training

Two experienced chiropractors, each with more than nine years of clinical experience, and two senior chiropractic students were observers. Five training sessions were completed prior to the actual study. This involved 15 patients, of which some had chest pain. The observers were instructed in the use of the protocol, and consensus was established regarding positive findings. Two chiropractors with more than three years of experience in using the protocol, including the creator of the protocol (HWC), acted as instructors.

2.3. Overall procedure

The standardized examination protocol comprises three parts: a semi-structured interview, a general health examination and a specific manual examination of the muscles and joints of the neck, thoracic spine and chest wall. Prior to the examination, patients answered self report questionnaires regarding patient demography, pain intensity, general health and quality of life (SF36 and EuroQol 5-D; The EuroQol Group, 1990; Bjorner et al., 1998a, b).

First, an experienced clinician, who did not take part in the reliability study, carried out the semi-structured interview. Results
of the interview and the patient questionnaires were then presented to the four observers in the reliability study. Subsequently, the four observers individually carried out the general health examination and specific manual examination of each patient in four successive sessions. (Fig. 1) Up to five patients were examined on each examination day. The order of the four observers was randomized on each examination day.

### 2.4. The standardized examination protocol

1. The semi-structured interview included pain characteristics, symptoms from the lungs and gastrointestinal system, past and present medical conditions, use of medication, psychosocial information and risk factors for ischemic heart disease. Patients were classified in accordance with Danish and international guidelines for angina pectoris (Haghfelt et al., 1996; Gibbons et al., 2002), Canadian Cardiovascular Society (Gibbons et al., 2002; Campeau, 1976), and NYHA (The Criteria Committee of the New York Heart Association, 2007).

2. The general health examination included blood pressure and pulse measurement, heart and lung stethoscopy, abdominal palpation, neck auscultation and neurological examination of the extremities. An orthopedic examination of the neck and shoulder joints was carried out in order to rule out nerve root compression syndromes.

3. The manual examination of the muscles and joints of the neck and the thoracic spine included active range of joint motion, palpation for segmental paraspinous muscular tenderness, motion palpation for joint-play restriction, end play restriction for thoracic facet and costo-vertebral joints, and manual palpation for muscular tenderness on 14 points of the anterior chest wall (Christensen et al., 2005). A sum score ranging from 14 to 42 for tenderness on the 14 points was calculated (1 point, no pain; 2 points, tenderness; 3 points, pain). The patients were asked whether the palpatory procedures caused discomfort or pain, and whether they recognized this pain or any symptom as comparable to the symptoms they felt at the admission to the department of cardiology.

Based on the complete procedure the observers independently had to answer the question, *does the patient have musculoskeletal chest pain? (yes/no)*, and mark findings of the individual tests. The observers were unaware of each other’s answers.

### 2.5. Statistical analyses

Cohen’s kappa was used to calculate the reliability of the binary examination variables (Landis and Koch, 1977). For continuous variables we used interclass correlation coefficient (ICC[2,1]) (Shrout and Fleiss, 1979). The descriptive terms proposed by Landis and Koch (1977) were used to interpret the kappa values, <0.00, poor; 0.00–0.20, slight; 0.21–0.40, fair; 0.41–0.60, moderate; 0.61–0.80, substantial; 0.81–1.00, almost perfect. ICCs were categorized as, <0.40, poor; 0.40–0.75, fair to good; >0.75, excellent. In this study, a kappa value equal to or higher than 0.60 was considered clinically acceptable. Analyses were performed using STATA (Stata Statistical Software: release 9.2. Stata Corp, College Station, TX, USA), except for ICCs which were calculated using SPSS (SPSS version 16.01. SPSS Inc. Chicago, IL, USA).

### 3. Results

Eighty subjects were included. Forty-five percent were female. The average age was 56 for women and 54 for men. The population characteristics concerning cardiovascular and pulmonary variables are shown in Table 2. Women more often had decline edema, a history of hypertension and a family history of coronary artery disease. Fifty percent of the subjects had a body mass index (BMI) above 27.7.

The prevalence of positive findings, percentage agreement and kappa values for each observer pair (chiropractors and students), as well as overall results for all four observers are shown in Tables 3 and 4. With respect to the overall musculoskeletal chest pain diagnosis (Table 3), the chiropractors reached substantial agreement, and the students reached moderate agreement. As shown in Table 3, student 1 was in agreement with the two chiropractors, whereas student 2 only reached a moderate level of agreement.

#### Table 2

<table>
<thead>
<tr>
<th>Variable</th>
<th>Gender (n/%)</th>
<th>Age, years [SD]</th>
<th>Hypercholesterolemia, n (%)</th>
<th>Hypertension, n (%)</th>
<th>Diabetes, n (%)</th>
<th>Smoking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, n (%)</td>
<td>36 (45)</td>
<td>56.2 [11.4]</td>
<td>13 (36.1)</td>
<td>15 (41.7)</td>
<td>3 (8.3)</td>
<td>9 (26.5)</td>
</tr>
<tr>
<td>Age, years [SD]</td>
<td>44 (55)</td>
<td>54.8 [12.1]</td>
<td>12 (27.3)</td>
<td>15 (34.1)</td>
<td>1 (2.3)</td>
<td>11 (25.0)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>3 (8.3)</td>
<td>30 [75]</td>
<td>39 [75]</td>
<td>39 [75]</td>
<td>4 [5.1]</td>
<td>29 [37.2]</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>80 (100)</td>
<td>55.5 [11.8]</td>
<td>39 [75]</td>
<td>39 [75]</td>
<td>4 [5.1]</td>
<td>29 [37.2]</td>
</tr>
<tr>
<td>Smoking</td>
<td>49 (61.3)</td>
<td>49 (61.3)</td>
<td>49 (61.3)</td>
<td>49 (61.3)</td>
<td>49 (61.3)</td>
<td>49 (61.3)</td>
</tr>
<tr>
<td>Presently, n (%)</td>
<td>32 (40)</td>
<td>36 (38.6)</td>
<td>36 (38.6)</td>
<td>36 (38.6)</td>
<td>36 (38.6)</td>
<td>36 (38.6)</td>
</tr>
<tr>
<td>Formerly, n (%)</td>
<td>24 (30)</td>
<td>25 (30)</td>
<td>25 (30)</td>
<td>25 (30)</td>
<td>25 (30)</td>
<td>25 (30)</td>
</tr>
<tr>
<td>Never, n (%)</td>
<td>30 (37.2)</td>
<td>24 (29.7)</td>
<td>24 (29.7)</td>
<td>24 (29.7)</td>
<td>24 (29.7)</td>
<td>24 (29.7)</td>
</tr>
<tr>
<td>Family history of ACS, n (%)</td>
<td>49 (61.3)</td>
<td>49 (61.3)</td>
<td>49 (61.3)</td>
<td>49 (61.3)</td>
<td>49 (61.3)</td>
<td>49 (61.3)</td>
</tr>
<tr>
<td>Height, cm [SD]</td>
<td>172.6 [10.6]</td>
<td>179.7 [7.8]</td>
<td>179.7 [7.8]</td>
<td>179.7 [7.8]</td>
<td>179.7 [7.8]</td>
<td>179.7 [7.8]</td>
</tr>
</tbody>
</table>
with the other three observers. The prevalence of musculoskeletal chest pain was fairly consistent for all four observers (range = [43.1–47.0%]).

When looking at agreement regarding individual binary outcomes, both chiropractors and students showed fair to substantial agreement regarding pain provocation tests (symptoms from the anterior chest wall, muscular tenderness from the chest wall, and symptoms from the paraspinal muscles).

Contrary to this, observer pairs showed poor to fair agreement for assessment of motion. It is worth noticing that the prevalence of positive findings was very high for presence of segmental biomechanical dysfunction and pain provocation tests (82%–95% and 52%–89%, respectively). In contrast, prevalence of neurologic and orthopedic tests was low (5%–11% and 0%–22%, respectively).

The continuous data are described in Table 4. In the assessment of blood pressure and heart rate, excellent agreement was seen (ICC = 0.77–0.93) for both examination pairs and overall. Agreement concerning the anterior chest pain score was fair to good (ICC = 0.52–0.63) for the chiropractors, students and all four examiners.

### Table 3
Agreement of the musculoskeletal chest pain diagnosis (Kappa [95% CI]).

<table>
<thead>
<tr>
<th></th>
<th>Chiropractor 2</th>
<th>Student 1</th>
<th>Student 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 74)</td>
<td>(n = 80)</td>
<td>(n = 65)</td>
</tr>
<tr>
<td>Chiropractor 1</td>
<td>0.73 [0.51;0.86]</td>
<td>0.76 [0.56;0.87]</td>
<td>0.43 [0.16;0.64]</td>
</tr>
<tr>
<td>(n = 66)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chiropractor 2</td>
<td>0.72 [0.53;0.85]</td>
<td>0.48 [0.23;0.67]</td>
<td></td>
</tr>
<tr>
<td>Student 1</td>
<td>0.47 [0.24;0.66]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Average prevalence of positive findings = 44.0% (SD = 4.3). Range [43.1–47.0%].

### Table 4
Paired and average agreement for all observers.

<table>
<thead>
<tr>
<th>Examination findings</th>
<th>Prevalence of positive findings (%)</th>
<th>Paired agreement</th>
<th>Average observer agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Chiropractor</td>
<td>Student</td>
<td>Chiropractors</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Overall assessment</td>
<td>Musculoskeletal chest pain</td>
<td>47.0</td>
<td>43.2</td>
</tr>
<tr>
<td>Pain provocation</td>
<td>Muscular tenderness on anterior chest wall</td>
<td>89.4</td>
<td>77.0</td>
</tr>
<tr>
<td></td>
<td>Symptoms on anterior chest wall</td>
<td>78.9</td>
<td>70.3</td>
</tr>
<tr>
<td></td>
<td>Paraspinal muscles</td>
<td>76.9</td>
<td>52.1</td>
</tr>
<tr>
<td>Orthopedic tests</td>
<td>Foramen compression test</td>
<td>0.0</td>
<td>19.0</td>
</tr>
<tr>
<td></td>
<td>Straight leg raise</td>
<td>1.8</td>
<td>4.1</td>
</tr>
<tr>
<td></td>
<td>Adson’s test</td>
<td>1.6</td>
<td>21.6</td>
</tr>
<tr>
<td>Assessment of motion</td>
<td>Shoulder range of motion</td>
<td>20.0</td>
<td>16.3</td>
</tr>
<tr>
<td></td>
<td>Cervical range of motion</td>
<td>35.0</td>
<td>33.8</td>
</tr>
<tr>
<td></td>
<td>Thoracic range of motion</td>
<td>5.0</td>
<td>8.8</td>
</tr>
<tr>
<td></td>
<td>Static springing test</td>
<td>89.2</td>
<td>41.9</td>
</tr>
<tr>
<td></td>
<td>Segmental biomechanical dysfunction</td>
<td>95.5</td>
<td>82.4</td>
</tr>
<tr>
<td></td>
<td>Neurologic examination</td>
<td>5.0</td>
<td>15.0</td>
</tr>
<tr>
<td></td>
<td>Average values</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anterior chest pain score (SD)</td>
<td>20.5 (4.4)</td>
<td>20.5 (5.7)</td>
</tr>
<tr>
<td></td>
<td>General health</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Systolic blood pressure, mmHg (SD)</td>
<td>138.1</td>
<td>146.0</td>
</tr>
<tr>
<td></td>
<td>(14.7)</td>
<td>(18.4)</td>
<td>(15.2)</td>
</tr>
<tr>
<td></td>
<td>Diastolic blood pressure, mmHg (SD)</td>
<td>86.7 (10.1)</td>
<td>92.4 (12.2)</td>
</tr>
<tr>
<td></td>
<td>(80.9)</td>
<td>(89.5)</td>
<td>(71.0)</td>
</tr>
<tr>
<td></td>
<td>Heart rate, bpm (SD)</td>
<td>64.0 (10.2)</td>
<td>68.0 (11.9)</td>
</tr>
</tbody>
</table>

The neurological examination of the upper extremity contained sensory examination, muscle strength and tendon reflex evaluation. In the lower extremity only tendon reflexes were evaluated. SD = Standard Deviation.
assessments of motion and neurologic examination ranges from poor to fair for all pairs of observers. These findings are all in line with the conclusions of the reviews and with overall results of classification systems used in neck and low back pain (Fritz et al., 2006; Trudelle-Jackson et al., 2008).

Different words and schemes have been used to evaluate strength of reproducibility, but there are no guidelines for interpreting good agreement (Landis and Koch, 1977; Haas, 1991). In studies of manual medicine, the level of acceptable clinical relevance has traditionally and somewhat arbitrarily been set at kappa above 0.40 (Stochkendahl et al., 2006), but the clinical context in which a procedure takes place has been argued to be a modifier (Myburgh et al., 2008). In chest pain, differential diagnosis includes pain of cardiac, pulmonary, gastroenterological, soft tissue, psychogenic and musculoskeletal origin, and more than one condition may be present complicating diagnosis (Eslick et al., 2005).

In this scenario, we asked the observers to decide on the presence or absence of musculoskeletal chest pain. However, in clinical practice, some degree of uncertainty about a diagnosis is common, as is operating with several working diagnoses; neither was an option in this research setting. Additionally, musculoskeletal chest pain is considered a disorder of benign origin, but with the potential to critically intrude in daily life, and a disorder in which management follows a rather heuristic pathway. Consequently, we considered kappa greater or equal to 0.60 as acceptable.

The importance of observer experience on reliability has been another subject of frequent discussion. One argument is that experienced observers have a tendency to develop individual interpretations of a test, which can reduce reliability (Mior et al., 1990; Hestbaek and Leboeuf-Yde, 2000). Others have argued against this saying that reliability is more dependent on consensus of positive findings than observer experience (Mootz et al., 1989; Mior et al., 1990; Hestbaek and Leboeuf-Yde, 2000; Seffinger et al., 2004). Our results suggest that experience affects the ability of observers to agree on the overall diagnosis, but not individual protocol components. This paradox can be explained by a difference in ability to process and interpret a series of findings. The observers in our study were familiar with the individual examination procedures, but none of them had previous experience in using the protocol as a whole. To reach consensus and minimize the risk of observers having a heterogeneous approach to the procedures, the observers practiced the protocol together and discussed definitions of positive findings. Nevertheless, it is possible that the clinical experience of the chiropractors aided in the decision-making process leading to a more consistent diagnostic procedure, and consequently, a higher reliability.

4.1. Limitations of this study

The standardized examination protocol consists of a patient interview and physical examination, but due to time constraints, solely a clinician not participating in the reliability study completed the patient interview. The four observers only carried out the physical examination. This was a logistic decision taken in order to decrease the length of each patient’s examination session.

Kappa is widely accepted as the statistical method of choice for evaluating agreement between two observers for a binary classification, but as discussed by Vach the composition of a study population can have a great impact on kappa (Vach, 2005). The higher the fraction of patients with very clear symptoms or very clear (palpation) findings, the easier it is for different observers to agree, and the easier it is to obtain high kappa values. It is hard to judge how many of the patients in the current population are easy to agree on and how many are difficult to agree on. However, as all patients in the current study have a history of acute chest pain and have been admitted to the emergency cardiology department with suspected acute coronary syndrome, and with the many differential diagnoses for acute coronary syndrome in mind, one may guess that the population does not include patients with very distinct symptoms in favor of musculoskeletal chest pain. Hence, this study population may be regarded more as a population with patients difficult to agree on than a population with patients easy to agree on.

Finally, this study did not include a group of non-trained observers. Thus, we are only able to evaluate the reliability following training sessions.

4.2. Implementation of protocol

The objective of this study was to determine whether the standardized examination protocol had an inter-observer reliability high enough to justify its use in the assessment of chest pain patients where a cardiac diagnosis had been ruled out. The protocol consists of case history and physical examination, and integration of both facets into an overall assessment brings the study protocol very close to clinical practice. The results from this study showed that the protocol had substantial inter-observer reliability in experienced observers, which should allow the implementation of the protocol into clinical practice. However, before this is allowed some criteria must be fulfilled:

- **Experience and training.** Our results suggest that a common training on 15 patients may bring some inexperienced observers close to the level of more experienced ones, whereas longer training may be needed for others. The results also indicate that even experienced observers do not agree perfectly. Hence, in either case, this suggests the need for implementation of a protocol training-program at both pre- and post-graduate levels.

- **Validation.** No golden standard has yet been determined for the evaluation of musculoskeletal chest pain. Therefore, we cannot be certain that a clinician-based diagnosis of musculoskeletal chest pain does indeed identify such patients.

- **Patients.** Prior to our examination, the patients included in this study were evaluated for acute coronary syndrome and carefully selected following inclusion and exclusion criteria. The protocol needs to be tested in other populations of patients with chest pain before full implementation can be recommended.

In the absence of a golden standard for the diagnosis of musculoskeletal chest pain, only an indirect validation of the protocol is possible. An attempt to indirectly validate the protocol is currently being undertaken through a randomized controlled trial using this protocol to identify participants with musculoskeletal chest pain (Stochkendahl et al., 2008). Future implementation of the standardized examination protocol is dependent on both the implementation of protocol training and further work on the validation of the diagnosis.

5. Conclusion

Suspected musculoskeletal chest pain can be identified with substantial inter-observer reliability using this standardized protocol if used by experienced and trained observers. Agreement for individual components of the protocol showed, however, considerable variation ranging from poor to substantial.
E. Paper V
Chiropractic treatment versus self-management in acute musculoskeletal chest pain in patients without acute coronary syndrome. A randomised controlled trial.

Mette Jensen Stochkendahl, MSc¹,²; Henrik Wulff Christensen, DC, MD, PhD²; Werner Vach, PhD³; Poul F. Høilund-Carlsen, MD, DMS⁴; Torben Haghfelt, MD, DMS⁵; Jan Hartvigsen, DC, PhD¹,².

3. Clinical Epidemiology, Institute of Medical Biometry and Medical Informatics, University Medical Centre Freiburg, Germany.
4. Department of Nuclear Medicine, Odense University Hospital.
5. Department of Cardiology, Odense University Hospital.
ABSTRACT

Summary of background data: The musculoskeletal system is a common, but often overlooked cause of chest pain. A previous uncontrolled study suggested beneficial effect of chiropractic therapy in patients with known or suspected stable angina pectoris.

Objectives: To evaluate in a randomised design the relative effectiveness of two treatment approaches for acute episodes of musculoskeletal chest pain, 1) a spinal manipulation-based approach as a typical example of chiropractic treatment and 2) self-management as an example of minimal intervention.

Design: Outcome assessor-blinded, randomised controlled trial using a computer generated randomisation schedule with mixed blocks of varying size.

Setting: Emergency cardiology department and four chiropractic clinics.

Participants: 115 consecutive patients presenting with acute chest pain and dismissed without a diagnosis of acute coronary syndrome.

Interventions: After baseline evaluation, patients with demonstrated musculoskeletal chest pain were randomized to four weeks of chiropractic treatment at community based chiropractic clinics (n=59) or to self-management (n=56). Questionnaire follow-up was made at 4 and 12 weeks.

Main outcome measures: Primary outcome measures were numeric change in pain intensity (11-point box numerical rating scale) and self-perceived change in pain (7-point ordinal scale). Secondary measures included Medical Outcomes Study Short Form 36 (SF-36) scores, change in pain intensity (chest, thoracic spine, neck and shoulder/arm), and self-perceived change in general health. Patients’ expectations to treatment effect were collected prior to randomisation.

Results: 58/49 chiropractic and 47/47 self-management patients were analysed at 4 and 12 weeks, respectively. Both groups experienced decreases in pain, self-perceived positive changes, and increases in SF36 scores. Observed between-group significant differences were in favour of chiropractic treatment, at 4 weeks regarding the primary outcome self-perceived change in pain (p=0.0013), at 12 weeks with respect to the primary outcome numeric change in pain intensity (Δ=1.10, p=0.022). In the chiropractic treatment group, 44 patients reported occasional side effects in form of local soreness, headache and fatigue of less than 24 hours duration.

Conclusions: This is the first randomised trial assessing chiropractic treatment versus minimal intervention in patients without acute coronary syndrome but with musculoskeletal chest pain. Results suggest that chiropractic treatment might be useful, but further research in relation to patient selection, standardisation of interventions and identification of potentially active ingredients is needed.

Trial registration: ClinicalTrials.gov NCT00462241
BACKGROUND

Acute chest pain is the hallmark of acute coronary syndrome (ACS) and accounts for 5-6% of all admissions to emergency departments in Europe and the US; however, only 20-25% of these admissions turn out to be caused by ACS.\textsuperscript{1-3} Between 1990 and 2000, most hospitals observed an increase in the overall number of admissions for suspected ACS, caused primarily by a doubling of patients with angina pectoris or undifferentiated chest pain.\textsuperscript{4} Patients with undifferentiated chest pain account for approximately 20% of admissions for suspected ACS.\textsuperscript{2,4,5} Commonly, they leave emergency departments without a definite diagnosis or a plausible explanation of their pain.\textsuperscript{6} Despite thorough diagnostic assessment, many continue to suffer from recurrent episodes of chest pain leading to anxiety, reduced quality of life, and frequent contacts to the health care system.\textsuperscript{7-10} In these patients, musculoskeletal dysfunction may be an overlooked source of pain,\textsuperscript{11} for which chiropractic treatment has been suggested beneficial in case reports.\textsuperscript{12-14} In 2004, our research group developed a standardised evaluation protocol to identify patients with musculoskeletal chest pain among patients with known or suspected stable angina pectoris, and treated them with chiropractic therapy in a non-randomised clinical trial.\textsuperscript{15,16} The results suggested that patients did benefit from chiropractic treatment, but the study did not allow to fully elucidate the value of chiropractic treatment in this category of patients, nor did it consider patients with acute chest pain.

The purpose of the present randomised controlled trial was to evaluate the relative effectiveness of two conservative treatment approaches in patients with an acute episode of musculoskeletal chest pain: 1) a spinal manipulation-based therapy as a typical example of chiropractic treatment and 2) self-management as an example of minimal intervention. Effectiveness was assessed by questionnaires 4 and 12 weeks after randomisation.

METHODS

Settings and participants

This study was carried out at an emergency cardiology department at a 1,000 bed urban, university hospital in Denmark and at four local chiropractic clinics from 6 August 2006 to 31 March 2008. The study was approved by the regional ethics committee of Vejle and Funen Counties, Denmark, approval number #VF 20060002, and registered at ClinicalTrials.gov, identification number NCT00462241.

In patients with an acute episode of chest pain, specialist cardiology nurses under cardiologist supervision were responsible for rapid diagnostic assessment for ACS using the electrocardiogram and biochemical cardiac marker testing, i.e., creatine kinase MB (mass) levels on admission and 6-9 hours later, and troponin T levels at least six hours after worst symptoms. The principal investigator (MJS) screened patient records of patients in whom a diagnosis of ACS or another definite cardiac or medical diagnosis could not be made, to identify eligible participants, i.e., patients aged 18-75 years who had a primary complaint of acute chest pain of less than seven days duration, were residents of the local county and could read and understand Danish. In addition, participants should have undergone diagnostic procedures to rule out ACS and should not have
significant co-morbidity or contraindications against spinal manipulative therapy. Not included were patients with previous or present ACS, prior percutaneous coronary intervention or coronary artery bypass grafting, inflammatory joint disease, insulin dependent diabetes, fibromyalgia, malignant disease, major osseous anomaly, osteoporosis, apoplexy or dementia, inability to cooperate, pregnancy, and chest pain from other definite cardiac or non-cardiac cause. In each case the cause for exclusion was noted.

**Trial procedures**
After being discharged from the emergency cardiology department and providing written informed consent, the participants were assessed at baseline by the first author using a standardised and previously validated study protocol.\textsuperscript{15,17} The protocol involves case history and clinical health examination, including manual examination of the spine and chest wall, in order to diagnose possible musculoskeletal chest pain. Demographic and clinical information was collected through patient self-report questionnaires and checklists for the study clinician. Detailed trial procedures are described elsewhere.\textsuperscript{18}

**Randomisation and blinding**
Only patients with a positive diagnosis of musculoskeletal chest pain were eligible for randomisation. The randomisation schedule was computer generated by a researcher not involved in the study and concealed from the study team. Consecutively numbered opaque and sealed envelopes with treatment assignment cards were created using a 1:1 allocation ratio and randomly mixed blocks of varying size. As patients became eligible, the envelopes were opened in consecutive order in the presence of the patient.

**Description of Interventions**
Two typical usual care management strategies for patients with musculoskeletal chest pain were chosen for this study: spinal manipulation-based therapy as an example of chiropractic treatment and self-management as an example of minimal intervention.

**Chiropractic treatment program**
Participants in the chiropractic treatment group were assigned to one of eight experienced chiropractors in their local community. Based on a combination of case history, clinical findings, and pragmatic, daily clinical practice, each chiropractor chose an individual treatment strategy accommodating age and physical condition of each patient. However, treatment had to include high-velocity low-amplitude manipulation directed towards the thoracic and/or cervical spine and could be combined with any of the following: Joint mobilisation, soft tissue techniques, stretching, stabilising or strengthening exercises, heat or cold treatment, and advice at the discretion of the treating clinician. A maximum of ten treatment sessions of approximately 20 minutes’ duration each, one to three times per week for four weeks was allowed. If the patient was pain free sooner, the treating chiropractor was free to discharge the patient. The chiropractors recorded the types of treatment given after each session, as well as any side effects experienced by the patient.
Self-management program
Immediately following group allocation, the study clinician gave participants in the self-management group a 15-minute consultation consisting of reassurance and advice directed towards promoting self-management. The content of this consultation was prepared with a senior cardiologist (TH). The study clinician (MJS) told participants that their chest pain generally had a benign, self-limiting course and based on the clinical evaluation gave individual instructions regarding posture and two to three home exercises aiming at increasing spinal movement or muscle stretch. She instructed participants to seek medical attention for re-evaluation (general practitioner, cardiology or emergency department) in case of severe or unfamiliar chest pain. Further, participants in this group were asked to refrain from seeking any type of manual treatment directed towards the muscles and joints of the thorax for the next four weeks.

Follow-up procedures
In the chiropractic group, a receptionist in the waiting room administered a self-report questionnaire to the patients at 4 weeks post randomisation after the final chiropractic treatment session. The questionnaire was returned immediately in a sealed envelope. At 12 weeks, a second questionnaire was administered by postal mail. In the self-management group, patients received self-report questionnaires by postal mail at 4 and 12 weeks. Questionnaires were resent to non-responders at eight and 12 weeks, and 16 and 20 weeks.

Outcome measures
Two primary outcome measures chosen \textit{a priori} were: 1) Change in pain intensity from baseline to follow-up (\textit{‘Rate your worst chest pain during the last seven days’}) offering at both times an 11-point box numeric rating scale, and 2) Self-perceived change in pain at follow-up (\textit{‘How is your pain now compared to what it was before you received treatment in this study?’}) using a 7-point ordinal scale with response categories ranging from ‘much worse’ to ‘much better’ with the category ‘unchanged’ in the middle.

Secondary outcome measures included Medical Outcomes Study Short Form 36-item Health Survey (SF-36) score, five measures of change in pain intensity (\textit{‘chest pain now’}, \textit{‘average chest pain’}, \textit{‘thoracic spine pain’}, \textit{‘neck pain’}, and \textit{‘shoulder-arm pain’} reported as average intensities during the last week), and self-perceived change in general health. Description of the outcome measures was reported elsewhere. To gauge the possible influence of patient expectations on treatment outcome, we collected information on expectations prior to randomisation.

Sample size
After obtaining the results with respect to the 4-weeks assessment of the self-perceived change in 31 patients, we inspected the difference in distribution between the two groups without knowing the group labels. Taking these distributions as the true one, a sample of 120 patients provided an 81% power that a Wilcoxon rank sum test would detect a shift in the distribution.
**Statistical analysis**

Baseline characteristics were reported as percentages for binary and categorical variables, and as means and standard deviations for continuous variables. Presence and change in presence of pain from baseline and to follow-up measurements at 4 and 12 weeks were calculated in absolute numbers and percentages, and compared within and between groups; within groups, we used the McNemar test to compare follow-up rates with baseline rates, and between groups, we used the Wilcoxon rank sum test. The analysis of change in pain intensity was restricted to patients with pain at baseline. We computed means and standard deviations in each treatment group and the differences in mean values with a t-test based 95% confidence interval. The main analyses of change in pain intensity, including p-values, were adjusted for baseline differences using ANCOVA. Ratings of the self-perceived change in pain were reported in absolute numbers and percentages and compared between the two groups using a Wilcoxon rank sum test. The statistical analyses were performed on the basis of the intention-to-treat principle, i.e. patients were analysed in the group to which they were allocated. Per protocol analysis, excluding all patients with deviations from the protocol, and as treated analysis were performed repeating the original analyses. In a secondary analysis, the correlation between patients' expectation and their self-perceived change in chest pain, as well as the difference between the two arms in expectation to the received treatment were compared using the paired t-test for baseline differences and the Spearman rank correlation coefficient to evaluate correlations. Analyses were performed using STATA (Stata Statistical Software: release 9.2. Stata Corp, College Station, TX, USA).

**RESULTS**

**Participants**

A detailed summary of patient recruitment, participation, and attrition is provided in Figure 1. In summary, 458 patients were eligible for baseline evaluation and 309 consented to participation. Of these, 115 met the inclusion criteria and were randomised: 59 to the chiropractic treatment group and 56 to the self-management group. Demographic and clinical characteristics of randomised participants are summarised in Table 1.

Randomisation resulted in two groups clinically comparable on baseline values. One participant in the chiropractic treatment group was dismissed without treatment by the treating chiropractor at the first visit, because he found no indication for manual therapy, and one patient discontinued treatment due to time constraints. The remaining 57 participants were seen by the chiropractors on average seven times [range: 2-10 consultations]. In the self-management group, all completed the information session.

**Chiropractic treatment**

All patients in the chiropractic treatment group received high-velocity low-amplitude spinal manipulative therapy, most often directed towards the mid thoracic region (Th4 to Th6 with adjoining costae) and the lower cervical spine (C6-C7). Trigger point therapy and massage were the
second most commonly used treatment modalities (n=56 patients, 95%). These were most often applied in the anterior, left side of the thorax and the trapezius muscles. In addition, a wide range of manual modalities, exercises and advice were applied, adapted to each individual patient. Side effects, affecting 44 patients, were transient and benign in nature, most commonly in the form of locally increased tenderness, headache or fatigue. No serious side effects lasting longer than 24 hours were reported.

**Presence and change in presence of pain**

At 4 and 12 weeks in both groups, the reduction in number with *worst chest pain* was statistically significant when compared to baseline with a further decrease from 4 to 12 weeks (Table 2). At both follow-up points the proportion that had improved in the chiropractic treatment group was slightly higher than in the self-management group (at 4 weeks: 14 (26%) vs. 9 (20%), p=0.48; at 12 weeks: 18 (38%) vs. 14 (30%), p=0.30), but between-group differences were non-significant.

With regard to the five secondary outcomes, especially in the chiropractic treatment group, similar patterns were observed for *chest pain now* and *average chest pain*, i.e., stepwise significant reductions in absolute numbers from baseline to 4 and 12 weeks, but without significant differences between groups. For *thoracic spine pain* there was in the chiropractic treatment group no change at 4 weeks, but a significant decrease at 12 weeks, whereas in the self-management group there were small insignificant changes yielding at 12 weeks a statistically significant change (chiropractic vs. self-management at 4 weeks: 8 (14%) vs. 10 (22%), p=0.45; at 12 weeks: 14 (27%) vs. 7 (16%), p=0.021). For *neck pain* there was in both groups a statistically non-significant decrease at 4 weeks and only small non-significant changes at 12 weeks compared to baseline, and for *shoulder-arm pain* there were significant decreases in both groups at 4 weeks, but at 12 weeks only in the chiropractic treatment group compared to baseline (Table 2).

**Numeric change in pain intensity (Table 3)**

Both at 4 and 12 weeks, the largest decrease in *worst chest pain* was seen in the chiropractic treatment group with adjusted differences between the groups of 0.78 and 1.10, respectively, the latter being statistically significant (p=0.022).

For the secondary outcomes, a tendency towards a larger decrease in pain intensity was seen within the chiropractic treatment group in three out of five measures (*chest pain now, average chest pain* and *neck pain*) at 4 weeks and in the self-management group in two out of five (*thoracic spine* and *shoulder-arm pain*). At 12 weeks, a tendency to more pronounced differences between groups was seen, as the chiropractic treatment group experienced a larger decrease in four out of five pain measures. None of these differences were however statistically significant.

**Self-perceived change in pain (Table 4)**

At 4 weeks, we observed statistically significant better ratings in the chiropractic treatment group. Eighty-two percent (n=44) rated their chest pain as 'better' or 'much better' compared to 60% (n=28) in the self-management group. Seven percent in the chiropractic treatment group (n=4) versus 32% (n=15) in the self-management group rated their chest pain as unchanged. One
participant in the chiropractic treatment group rated the pain as ‘a little worse’ versus none in the self-management group. No participants reported ‘worse’ or ‘much worse’.

At 12 weeks, the difference in self-perceived change in pain was no longer statistically significant, because the self-management group rated slightly more positive than at 4 weeks with 35% (n=17) rating ‘much better’ and 17% (n=8) rating ‘better’ (vs. 23% (n=11) and 36% (n=17) at 4 weeks). Ten percent (n=5) in the chiropractic treatment and 19% (n=9) in the self-management group were unchanged. Self-perceived change in general health and overall treatment effect showed similar results with statistically non-significant differences in favour of the chiropractic treatment group.

Quality of life scores (SF36)
Except for social function in the chiropractic treatment group at 4 weeks, both groups experienced improvements in all eight domains at 4 and 12 weeks (data not shown). No specific trend or statistically significant differences in either direction between groups were found.

Analysis of sensitivity of results
Despite requesting the participants in the self-management group to refrain from manual therapy, five participants received chiropractic treatment within four weeks of baseline. In addition, one patient in the chiropractic treatment group did not initiate treatment. However, the results of the as-treated and per protocol analyses (data not shown) did not alter any the conclusions of the intention-to-treat analyses.

Patients’ expectations
We examined the relationship between the patients’ expectation to either treatment and their self-perceived change in pain at both time points and found no statistically significant correlations (at 4 weeks: chiropractic treatment r=-0.05, p=0.57; self-management r=0.15, p=0.13; at 12 weeks chiropractic treatment r=0.11, p=0.31; self-management r=0.26, p=0.01). There was no statistically significant difference between expectations to the actual treatment received between the two groups (chiropractic treatment: mean=2.21 vs. self-management mean=2.31, p=0.37).

DISCUSSION
We report on the first randomised trial evaluating the effect of chiropractic treatment of musculoskeletal chest pain in patients dismissed from a cardiac emergency department without a diagnosis of ACS when this is compared to a minimal intervention. In both groups we found decrease in pain intensity and in the proportion of patients with pain, self-perceived positive changes in pain, and increases in SF36, all reflecting better health and wellbeing. At statistically significant levels, chiropractic treatment was favoured by the primary outcomes ‘self-perceived change in pain’ and ‘numeric change in pain intensity’ at 4 and 12 weeks, respectively. The majority of the non-significant results was also in favour of the chiropractic treatment group.
Interpretation of results

The tendency of results in favour of the chiropractic treatment group was consistent at both follow-up points, and a closer look reveals interesting patterns. Both groups experienced reduction in worst chest pain intensity (Table 3), but with a tendency to slightly larger difference between groups through follow-up mainly due to a larger reduction in the chiropractic treatment group. This tendency was noted for four of six measures of pain intensity. The chiropractic treatment group reported an increase in pain intensity at 4 weeks for average thoracic spine pain followed by a relatively larger reduction at 12 weeks follow-up, probably reflecting less local soreness, which was often reported in the chiropractic treatment group. Caused primarily by a more positive rating by the self-management group at 12 compared to 4 weeks, an opposite pattern was seen for the subjective outcome (self-perceived change in pain) in which the smallest difference was noted at 12 weeks. As the level of pain intensity generally remained constant in the self-management group from 4 to 12 weeks, the change in self-perceived change in pain may reflect that. Despite continued pain, these patients gradually adapt to their situation. These results indicate that the time point at which the participants are asked about symptoms and treatment effect is important. Pain perception appears to be a dynamic process, and pain intensity and self-perceived change in pain may be rated independently of each other. Even though group differences were small, the improvement in pain intensity in both groups is substantial. One may argue that chiropractic treatment is an ‘add on’ perhaps leading to faster recovery than without treatment.

Previous research has documented intriguing associations between patients’ expectations for treatment benefits and their clinical outcome.\textsuperscript{21,22} In patients with low back pain, correlations between the patients’ expectation and the improvement obtained have been noted. Our patients' self-perceived change in pain correlated with patients' expectation, however only to a moderate degree. There was no difference in the expectation between the two treatment groups, and therefore a priori expectations were unlikely to cause bias in this trial. Generally, participants had positive expectations to both treatment groups as opposed to patients who declined participation, who often expressed negative expectations toward chiropractic treatment. As a consequence, study results may not be representative for non-participants. The same tendency was noted previously by Christensen et al.\textsuperscript{16} who found that refusal to participate was due to either a negative expectation towards chiropractic treatment or an ongoing belief that heart disease had not been ruled out even when all cardiac examinations were normal.

Strengths

The chiropractic treatment was given in community based chiropractic clinics by eight different chiropractors each treating their group of participants. Therefore, observed effects were independent of a single care provider, and our findings may have good generalised validity, in particular because treatment was personalised and given at the discretion of each chiropractor.

As recommended for studies of pain\textsuperscript{23} we assessed several patient-rated variables. Pain intensity and self-perceived change in pain were chosen a priori as the primary outcomes as these are considered the most important outcomes in patients with a variety of pain syndromes, along with quality of life.\textsuperscript{23} Global rating scales are regarded as clinically relevant and responsive to measure patients’ perceived recovery.\textsuperscript{24}
The diagnosis of musculoskeletal chest pain was based on systematic patient assessment using a standardized protocol showing substantial inter-observer agreement. The issue of validity of this diagnosis has been addressed previously by us in patients with stable angina pectoris in whom an experienced clinician could fairly convincingly identify a subset of patients with musculoskeletal chest pain. In the present study, positive response to treatment targeted at structures believed to be pain generators (muscles and joints of the cervicothoracic spine and chest wall) gave further support to the validity of the diagnosis. In addition, we feel our multidisciplinary research team comprising experts in cardiology, clinical physiology, chiropractic, and biostatistics may have served as a shield against one-eyed interpretations.

Limitations
Musculoskeletal chest pain is a clinical diagnosis without a golden standard, and its presence is difficult to confirm. Thus the diagnosis is susceptible to inter-observer variation. The pragmatic design of our study did not allow for standardisation of treatment or identification of active ingredients of the interventions. The decrease in pain in both groups might therefore be a result of regression towards the mean, however this cannot explain group differences.

The protocol used to identify patients with musculoskeletal chest pain was not designed to classify or exclude other potential causes of chest pain, and thus, we could not allege musculoskeletal chest pain as the sole cause of chest discomfort. Gastro-oesophageal reflux disease (GERD) is probably the most common differential diagnosis, but due to constraints, specific examination for GERD was not possible, nor did we examine for overlap with other causes of non-specific chest pain, e.g., anxiety and depression. These causes may have influenced and limited the benefit of the interventions.

We included patients with an acute episode of chest pain and found that the population comprised patients with both first time and repeated episodes. The two groups may not respond equally well to spinal manipulative therapy, and focusing on patients with first-time symptoms may reveal larger treatment effects.

In addition, approximately 15% of participants in the self-management group at 4 weeks and in both groups at 12 weeks did not return their questionnaires, and side effects were only queried in the chiropractic treatment group. Finally, there is a general uncertainty regarding the outcome measures of the disease-unspecific measure ‘pain’ and its clinical implications.

Lessons learned and questions to be answered
The combined research effort of participants from such diverse fields as chiropractic and cardiology was a challenge and an eye-opener to all. These results illustrate how open-mindedness and multidisciplinarity can help bring forward clinically relevant answers to complex areas such as undifferentiated chest pain.

Discomfort, shortness of breath, anxiety, fear, and depression are other aspects of an acute chest pain episode that may lead to or contribute to admission in this category of patients. Such aspects were not explored in this study. Clarification of what aspects of the pain episode patients consider important may be needed to schedule appropriate treatment.
With the small group differences, study limitations, and unresolved issues in mind, the question remains whether active chiropractic treatment leads to faster recovery and is worth the additional cost. One the other hand, the scale of the problem in terms of number of patients concerned, the documented consequences in daily life and repeated contact to the health care system for those affected certainly justify intervention to minimize suffering and cost. However, before implementation, definitions and personalised manual therapy regimens should be tested alone or in combination with other treatment modalities to estimate the potential gain of a chiropractic approach to managing musculoskeletal chest pain.

**CONCLUSIONS**

We conducted what we believe is the first randomised controlled trial assessing chiropractic treatment of acute musculoskeletal chest pain compared to self-management in patients dismissed from an emergency clinic without a diagnosis of ACS. With both regimens, we observed substantial decreases in pain, however, with statistically significant and non-significant differences in favour of the chiropractic group. The active ingredients in either treatment are unknown and regression towards the mean probably play a role. The tendencies and trends in favour of chiropractic treatment should encourage further research to examine exactly what role chiropractic treatment may play in patients with acute chest pain of musculoskeletal origin.
REFERENCES


**Figure 1.** Participant flow through trial

- **Assessed for eligibility (n=4433)**
  - Excluded (n=3975)
    - Not meeting inclusion criteria (n=3975)

- **Eligible for baseline evaluation (n=458)**
  - Excluded (n=149)
    - Refused to participate (n=50)
    - Not able to contact (n=86)
    - Did not show for appointment (n=13)

- **Baseline evaluation (n=309)**
  - Excluded from RCT (n=194)
    - Not meeting inclusion criteria (n=190)
    - Other reasons (n=4)

**Randomised (n=115)**

- **Allocated to Chiropractic treatment (CT) (n=59)**
  - Received CT (n=58)
  - Did not receive CT (n=1)
    - Reason: Chiropractor found no indication for SMT
  - Lost to follow-up
    - Week 4 (n=0)
    - Week 12 (n=8)
  - *Discontinued CT (n=1)
    - Reasons:
      - Time commitment (n=1)

- **Allocated to Self-management (SM) (n=56)**
  - Received SM (n=56)
  - Did not receive SM (n=0)
  - Lost to follow-up
    - Week 4 (n=9)
    - Week 12 (n=8)
  - *Discontinued SM (n=0)

- **Analyzed**
  - Week 4 (n=58)
  - Week 12 (n=51)
  - Analyzed
    - Week 4 (n=47)
    - Week 12 (n=48)
Table 1. Baseline patient characteristics. Data is expressed as means and standard deviations (±SD) or absolute numbers and relative frequencies (in parentheses).

<table>
<thead>
<tr>
<th></th>
<th>Chiropractic treatment</th>
<th>Self-management</th>
<th>Total</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 59</td>
<td>n = 56</td>
<td>n = 115</td>
<td></td>
</tr>
<tr>
<td>Age, years ±SD</td>
<td>51.4 ± 10.0</td>
<td>50.8 ± 12.1</td>
<td>51.1 ± 11.0</td>
<td>0.77</td>
</tr>
<tr>
<td>Female, n(%)</td>
<td>26 (44.0)</td>
<td>22 (39.3)</td>
<td>48 (41.7)</td>
<td>0.60</td>
</tr>
<tr>
<td>Body Mass Index, kg/m² ±SD</td>
<td>27.0 ± 4.6</td>
<td>27.8 ± 4.7</td>
<td>27.4 ± 4.7</td>
<td>0.38</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg ±SD</td>
<td>135.5 ± 18.2</td>
<td>136.2 ± 16.9</td>
<td>135.8 ± 17.5</td>
<td>0.82</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg ±SD</td>
<td>85.2 ± 10.8</td>
<td>87.0 ± 9.4</td>
<td>86.1 ± 10.1</td>
<td>0.34</td>
</tr>
<tr>
<td>Maximum chest pain, b ±SD</td>
<td>6.7 ± 2.4</td>
<td>5.9 ± 2.3</td>
<td>6.3 ± 2.4</td>
<td>0.076</td>
</tr>
<tr>
<td>SF36 Physical health component scale ±SD</td>
<td>44.5 ± 8.8</td>
<td>44.2 ± 8.9</td>
<td>44.4 ± 8.8</td>
<td>0.87</td>
</tr>
<tr>
<td>SF36 Mental health component scale ±SD</td>
<td>48.4 ± 8.9</td>
<td>45.8 ± 12.3</td>
<td>47.2 ± 10.7</td>
<td>0.21</td>
</tr>
<tr>
<td>Risk factors of ischemic heart disease c</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker, n(%)</td>
<td>16 (29.6)</td>
<td>16 (28.6)</td>
<td>32 (29.1)</td>
<td>0.90</td>
</tr>
<tr>
<td>Hypercholesterolemia, n(%)</td>
<td>15 (25.9)</td>
<td>15 (26.8)</td>
<td>30 (26.3)</td>
<td>0.91</td>
</tr>
<tr>
<td>Hypertension, n(%)</td>
<td>12 (20.7)</td>
<td>15 (26.8)</td>
<td>27 (23.7)</td>
<td>0.44</td>
</tr>
<tr>
<td>Diabetes, n(%)</td>
<td>1 (1.7)</td>
<td>3 (5.5)</td>
<td>4 (3.5)</td>
<td>0.28</td>
</tr>
<tr>
<td>Previous episodes of chest pain, n(%)</td>
<td>39 (67.2)</td>
<td>41 (73.2)</td>
<td>80 (70.2)</td>
<td>0.49</td>
</tr>
<tr>
<td>Engaging in daily light exercise, n(%)</td>
<td>25 (49.0)</td>
<td>22 (44.9)</td>
<td>47 (47.0)</td>
<td>0.68</td>
</tr>
<tr>
<td>Engaging in daily heavy exercise, n(%)</td>
<td>3 (13.0)</td>
<td>2 (7.7)</td>
<td>5 (10.2)</td>
<td>0.54</td>
</tr>
<tr>
<td>Married/living with someone, n(%)</td>
<td>51 (86.4)</td>
<td>50 (90.9)</td>
<td>101 (88.6)</td>
<td>0.45</td>
</tr>
<tr>
<td>Working, n(%)</td>
<td>44 (75.9)</td>
<td>35 (63.6)</td>
<td>79 (69.9)</td>
<td>0.16</td>
</tr>
<tr>
<td>College graduate, n(%)</td>
<td>16 (27.6)</td>
<td>16 (30.2)</td>
<td>32 (28.8)</td>
<td>0.76</td>
</tr>
<tr>
<td>Expectation of treatment d</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chiropractic treatment ±SD</td>
<td>2.2 ± 0.5</td>
<td>2.1 ± 0.6</td>
<td>2.1 ± 0.6</td>
<td>0.52</td>
</tr>
<tr>
<td>Self-management ±SD</td>
<td>2.3 ± 0.5</td>
<td>2.3 ± 0.6</td>
<td>2.3 ± 0.5</td>
<td>0.81</td>
</tr>
</tbody>
</table>

* P-values were calculated using t-test for continues data, xhi² for categorical data and Wilcoxon ranksum test for ordinal data.

b Pain intensity was reported on an 11-point numeric rating scale ranging from 0: no pain to 10: worst possible pain.

c Risk factors were identified from the case history; in hypercholesterolemia, hypertension and diabetes, information was based on whether the patient was in medical treatment or the condition had previously been diagnosed.

d Expectation was reported as average ratings on a 5-point box scale (much better=1 to much worse=5)
Table 2. Frequencies of patients with pain at baseline responding at follow-up, within group comparisons at follow-up, absolute numbers and frequencies (in parentheses) of patients with change in presence of pain, and between group comparisons at four and 12 weeks follow-up.

<table>
<thead>
<tr>
<th>Complaint</th>
<th>Intervention</th>
<th>4 weeks follow-up</th>
<th></th>
<th>12 weeks follow-up</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n</td>
<td>% with pain</td>
<td>p&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Absolute numbers, n (%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Baseline</td>
<td>Follow-up</td>
<td>Improved</td>
<td>Deteriorated</td>
</tr>
<tr>
<td>Worst chest pain&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Chiropractic</td>
<td>55</td>
<td>100.0</td>
<td>74.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Self-manage</td>
<td>46</td>
<td>95.7</td>
<td>76.1</td>
<td>0.0027</td>
</tr>
<tr>
<td>Worst chest pain&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Chiropractic</td>
<td>55</td>
<td>77.6</td>
<td>49.1</td>
<td>0.0011</td>
</tr>
<tr>
<td></td>
<td>Self-manage</td>
<td>46</td>
<td>83.0</td>
<td>56.5</td>
<td>0.0027</td>
</tr>
<tr>
<td>Chest pain, average&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Chiropractic</td>
<td>55</td>
<td>94.6</td>
<td>72.7</td>
<td>0.0039</td>
</tr>
<tr>
<td></td>
<td>Self-manage</td>
<td>46</td>
<td>93.6</td>
<td>71.7</td>
<td>0.0016</td>
</tr>
<tr>
<td>Thoracic spine pain&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Chiropractic</td>
<td>58</td>
<td>62.1</td>
<td>62.1</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>Self-manage</td>
<td>47</td>
<td>53.3</td>
<td>44.7</td>
<td>0.47</td>
</tr>
<tr>
<td>Neck pain&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Chiropractic</td>
<td>58</td>
<td>60.3</td>
<td>55.2</td>
<td>0.56</td>
</tr>
<tr>
<td></td>
<td>Self-manage</td>
<td>47</td>
<td>69.6</td>
<td>44.8</td>
<td>0.16</td>
</tr>
<tr>
<td>Shoulder-arm pain&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Chiropractic</td>
<td>58</td>
<td>78.6</td>
<td>52.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Self-manage</td>
<td>47</td>
<td>78.3</td>
<td>47.5</td>
<td>0.033</td>
</tr>
</tbody>
</table>

a. Pain intensity was reported using an 11-point numeric rating scale ranging from 0 (no pain) to 10 (worst possible pain). Presence of pain indicates a score >0. ‘Improved’ indicates a shift from a score >0 at baseline to a score=0 at follow-up. ‘Deteriorated’ indicates a shift from no pain at baseline to a score >0 at follow-up. Worst chest pain was reported for the last seven days. Chest pain, average; thoracic spine pain; neck pain and shoulder-arm pain was reported as average pain during the last seven days.

b. Within group comparisons of frequencies of patients with pain at baseline vs. follow-up using McNemars test.

c. Between group comparisons of change in absolute numbers of patients with pain at follow-up using Wilcoxon rank sum test.
Table 3. Numeric change in pain intensity from baseline to follow-up in patients with pain at baseline responding at follow-up.

<table>
<thead>
<tr>
<th>Complaint</th>
<th>Intervention</th>
<th>n</th>
<th>Mean ±SD</th>
<th>Δ</th>
<th>95% CI</th>
<th>Adjusted differenceb</th>
<th>n</th>
<th>Mean ±SD</th>
<th>Δ</th>
<th>95% CI</th>
<th>Adjusted differenceb</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Worst Chest pain</strong></td>
<td>Chiropractic</td>
<td>55</td>
<td>3.95 ±2.97</td>
<td>1.10</td>
<td>[0.015; 2.19]</td>
<td>0.78 [0.15; 1.71]</td>
<td>48</td>
<td>4.77 ±2.61</td>
<td>1.53</td>
<td>[0.40; 2.66]</td>
<td>1.10 [0.16; 2.03]</td>
</tr>
<tr>
<td></td>
<td>Self-manage</td>
<td>44</td>
<td>2.84 ±2.36</td>
<td></td>
<td></td>
<td></td>
<td>45</td>
<td>3.24 ±2.88</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Chest pain, now</strong></td>
<td>Chiropractic</td>
<td>42</td>
<td>1.64 ±2.25</td>
<td>0.20</td>
<td>[-0.82; 1.21]</td>
<td>0.12 [0.72; 0.97]</td>
<td>36</td>
<td>2.33 ±2.33</td>
<td>0.44</td>
<td>[-0.64; 1.52]</td>
<td>0.26 [-0.52; 1.04]</td>
</tr>
<tr>
<td></td>
<td>Self-manage</td>
<td>38</td>
<td>1.45 ±2.29</td>
<td></td>
<td></td>
<td></td>
<td>39</td>
<td>1.90 ±2.36</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Chest pain, average</strong></td>
<td>Chiropractic</td>
<td>50</td>
<td>2.12 ±2.03</td>
<td>0.089</td>
<td>[-0.89; 0.71]</td>
<td>0.075 [-0.59; 0.74]</td>
<td>43</td>
<td>2.72 ±1.83</td>
<td>0.23</td>
<td>[-0.63; 1.09]</td>
<td>0.33 [-0.37; 1.04]</td>
</tr>
<tr>
<td></td>
<td>Self-manage</td>
<td>43</td>
<td>2.21 ±1.81</td>
<td></td>
<td></td>
<td></td>
<td>43</td>
<td>2.49 ±2.18</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Thoracic spine pain</strong></td>
<td>Chiropractic</td>
<td>36</td>
<td>1.28 ±3.12</td>
<td>-0.51</td>
<td>[-2.08; 1.05]</td>
<td>-0.24 [-1.32; 0.84]</td>
<td>32</td>
<td>2.09 ±2.44</td>
<td>0.80</td>
<td>[-0.56; 2.16]</td>
<td>0.87 [-0.25; 2.00]</td>
</tr>
<tr>
<td></td>
<td>Self-manage</td>
<td>24</td>
<td>1.79 ±2.70</td>
<td></td>
<td></td>
<td></td>
<td>24</td>
<td>1.29 ±2.61</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Neck pain</strong></td>
<td>Chiropractic</td>
<td>35</td>
<td>1.03 ±2.43</td>
<td>0.43</td>
<td>[-0.81; 1.68]</td>
<td>0.89 [-0.12; 1.89]</td>
<td>31</td>
<td>1.19 ±2.44</td>
<td>0.44</td>
<td>[-0.85; 1.72]</td>
<td>0.83 [-0.31; 1.97]</td>
</tr>
<tr>
<td></td>
<td>Self-manage</td>
<td>32</td>
<td>0.59 ±2.66</td>
<td></td>
<td></td>
<td></td>
<td>33</td>
<td>0.76 ±2.69</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Shoulder-arm pain</strong></td>
<td>Chiropractic</td>
<td>44</td>
<td>1.50 ±3.01</td>
<td>-0.25</td>
<td>[-1.43; 0.93]</td>
<td>-0.050 [-1.10; 1.00]</td>
<td>38</td>
<td>1.16 ±2.79</td>
<td>-0.45</td>
<td>[-1.67; 0.76]</td>
<td>-0.20 [-1.33; 0.93]</td>
</tr>
<tr>
<td></td>
<td>Self-manage</td>
<td>36</td>
<td>1.75 ±2.10</td>
<td></td>
<td></td>
<td></td>
<td>36</td>
<td>1.61 ±2.44</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a. Pain intensity was reported using an 11-point numeric rating scale ranging from 0 (no pain) to 10 (worst possible pain). Worst chest pain was reported for the last seven days.
   Chest pain, average; thoracic spine pain; neck pain and shoulder-arm pain was reported as average pain during the last seven days.
b. Between group differences adjusted for baseline differences in pain intensity.
Table 4. Patients’ self-perceived change in pain and general health, and patients’ perception of treatment effect at 4 and 12 weeks follow up.

<table>
<thead>
<tr>
<th>Variable</th>
<th>4 weeks</th>
<th>12 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Chiropractic treatment</td>
<td>Self-management</td>
</tr>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td><strong>How is your chest pain now compared to before treatment?</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Much better</td>
<td>28 (51.9)</td>
<td>11 (23.4)</td>
</tr>
<tr>
<td>Better</td>
<td>16 (29.6)</td>
<td>17 (36.2)</td>
</tr>
<tr>
<td>A little better</td>
<td>5 (9.3)</td>
<td>4 (8.5)</td>
</tr>
<tr>
<td>Unchanged</td>
<td>4 (7.4)</td>
<td>15 (31.9)</td>
</tr>
<tr>
<td>A little worse</td>
<td>1 (1.9)</td>
<td>0</td>
</tr>
<tr>
<td>Worse</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Much worse</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>How is your general health now compared to before treatment?</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Much better</td>
<td>15 (27.3)</td>
<td>5 (10.6)</td>
</tr>
<tr>
<td>Better</td>
<td>23 (41.8)</td>
<td>10 (21.3)</td>
</tr>
<tr>
<td>A little better</td>
<td>7 (12.7)</td>
<td>11 (23.4)</td>
</tr>
<tr>
<td>Unchanged</td>
<td>9 (16.4)</td>
<td>20 (42.6)</td>
</tr>
<tr>
<td>A little worse</td>
<td>1 (1.8)</td>
<td>1 (2.1)</td>
</tr>
<tr>
<td>Worse</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Much worse</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Did the treatment help?</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Helped a lot</td>
<td>35 (63.6)</td>
<td>14 (30.0)</td>
</tr>
<tr>
<td>Helped some</td>
<td>17 (30.9)</td>
<td>27 (57.5)</td>
</tr>
<tr>
<td>Did not help</td>
<td>2 (3.6)</td>
<td>6 (12.8)</td>
</tr>
<tr>
<td>Got worse</td>
<td>1 (1.8)</td>
<td>0</td>
</tr>
</tbody>
</table>

^a Wilcoxon rank sum test.