Risk scores: a guide in clinical practice?

Application of risk scores in the management of
Non-ST-Elevation Acute Coronary Syndromes

Josien Engel

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Voor opa

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1

General introduction

'In NST-ACS, quantitative assessment of ischemic risk by means of scores is superior to the clinical assessment alone' – European Society of Cardiology, 2015.

Evidence-based risk assessment is critical for selection of the optimal management strategy in non-ST-elevation acute coronary syndrome (NST-ACS) patients, and reduces unwarranted practice variation. Unwarranted practice variation is described as: "practice variation not explained by type or severity of illness, or by patient preferences", and can be a threat to patient safety [1]. International cardiac guidelines therefore recommend that physicians take into account multiple clinical factors (e.g. cardiac history, risk factors, troponin and electrocardiogram findings) when deciding upon appropriate treatment [2,3]. Besides the assessment of these clinical factors, the use of validated risk scoring instruments – in which among other the aforementioned clinical factors are combined – are recommended to guide clinical judgement. The physician can use a risk score to calculate a patient's risk of re-infarction or death, and subsequently can weigh the outcome with other clinical information in its choice of treatment. It has however been suggested before that physicians may have a skeptic attitude towards the use of risk scores in decision-making [4]. Although these instruments have been extensively validated and are recommended by renowned guidelines such as the European Society of Cardiology (ESC) and the American College of Cardiology/ American Heart Association (ACC/AHA) guidelines, it is unknown to what extent risk scores are used in practice and if they actually contribute to a cardiologist's decision-making. As several studies found that low(er) guideline adherence in NST-ACS was associated with worsened patient outcomes [5], it is important to identify a possible guideline-practice gap. Furthermore, it is important to identify factors contributing to this guideline-practice gap. These insights can serve to prioritize specific patient groups for future quality improvement initiatives, or to tailor these initiatives to present barriers and in that way enhance implementation-success of risk scores in clinical practice.

1.1 Evidence based quality improvement programs

Worldwide several large quality improvement programs have been initiated to monitor and improve guideline adherence in the management of non-ST-elevation acute coronary syndrome patients [6-10]. The latest ESC and ACC/AHA guidelines recommend hospitals to participate in these programs, to monitor performances on different clinical measures [2,3]. Indicators or performance measures are often used, in the context of quality improvement programs, to monitor care processes, or for benchmarking purposes [11]. In response to a large study regarding patient safety in Dutch hospitals [12], a nationwide quality improvement program was initiated in the Netherlands: VMSzorg [13]. This program aimed to improve safety of care for eleven identified patient safety threats. One of these threats concerned

the theme 'optimal care for acute coronary syndromes', which consisted of several quality indicators (Box 1.1) [14]. The rationale to prioritize this theme as one of eleven focus points of the improvement program, were the high number of deaths and hospital admissions related to ACS, and the effect of processes of care on patient's survival rates, in terms of improvements in timely and correct risk assessment and subsequent treatment.

Box 1.1 Performance indicators of the VMS Safety management program 'optimal care for acute coronary syndrome' theme

By the end of December 2012 all Dutch hospitals work according to the European Society of Cardiology (ESC) guidelines, by achieving the following objectives:

Structure
- All hospitals have a policy for referring eligible patients with ACS for cardiac rehabilitation;
- All hospitals provide cardiac rehabilitation programs, or have contracts with cardiac rehabilitation providers in their region.

Process
- In at least 90% of patients diagnosed with UA or NSTEMI treatment decisions are based on risk stratification, using the GRACE, TIMI or FRISC risk score, and are documented in the patients' chart;
- In at least 90% of patients with an acute STEMI treatment with percutaneous coronary intervention is started within 90 minutes after first paramedical contact;
- At least 90% of patients with ACS received the recommended medication at discharge, including aspirin, thienopyridine, beta-blocker, statin and ace-inhibitor.

Outcome
- 30-day mortality

1.2 Burden of coronary heart disease

Coronary heart diseases (CHD), including ACS, account for a large number of hospital admissions and deaths worldwide [15], and is in the top three of causes of death in The Netherlands [16]. Throughout the years, innovations in treatment practices, including percutaneous coronary intervention and the administration of preventive pharmacological therapies at discharge, have led to a significant reduction in mortality from CHD [17-19]. Despite these advancements, the number of deaths remain high, and CHD is expected to account for the largest disease burden worldwide by 2020 [20]. As a result, the management of this condition will continue to put a high burden on health care systems. In 2030, in the United States, total direct medical costs for CHD (i.e. all costs that result from inpatient and outpatient health services), are expected to be threefold from the current medical costs: from $35.7 billion to $106.4 billion [21]. In the Netherlands, the costs for CHD in 2011 were 2.1

billion euros and comprised 2.3 percent of the annual total health care costs [22]. The costs of treatment of CHD are thus substantial and have increased over the years.

1.2.1 Acute coronary syndromes

Among coronary heart disease are three sub-conditions, summed under the umbrella term acute coronary syndrome (ACS), i.e. ST-Elevation Myocardial Infarction (STEMI), Non-ST-Elevation Myocardial Infarction (NSTEMI) and Unstable Angina (UA). ACS refers to situations in which the patient's blood supply to the heart is narrowed or blocked by a thrombosis [2,3,23,24]. As a result, patients may experience complaints of chest pain. The classification of patients in STEMI, NSTEMI or UA is primarily based on electrocardiogram findings and on blood markers of myocardial necrosis i.e. biomarkers [2,3]. Patients are diagnosed with STEMI in case one or more of the coronary arteries are fully blocked, which is characterized by persistent ST-segment elevation on the electrocardiogram [25]. The diagnosis of NSTEMI or UA is less straightforward, especially in patients without typical symptoms or with no electrocardiographic findings suspicious for ischaemia [2,3]. In NSTEMI patients the blood supply to the heart muscle is reduced due to a partial or intermittent blockage of one or more of the coronary arteries, leading to ischaemia. To distinguish NSTEMI from UA, cardiac biomarkers (e.g. troponin measures) in the blood are determined. In case of a significant rise or fall of troponin levels over repeated measurements, patients are diagnosed with NSTEMI [2,3]. In case patients show typical symptoms of acute chest pain (in rest), but without changes in cardiac biomarkers or on the electrocardiogram, patients are diagnosed with UA [26,27].

Management strategies differ per sub-condition of ACS. Because the blood supply of the heart is blocked completely, STEMI patients require urgent revascularization to prevent further cardiac damage or dying [25]. Patients diagnosed with NST-ACS (i.e. NSTEMI or UA) receive treatment on the basis of results from serial electrocardiograms and measurements of cardiac biomarkers. In NST-ACS patients, there is more time for diagnostics compared to STEMI patients. However, on the longer term, these patients have a higher risk of (recurrent) myocardial infarction and death [28-31]. Initial treatment should be tailored to a patient's individual level of risk of major adverse cardiac events (e.g. myocardial infarction and/or death), to achieve an optimal balance between the risks and benefits of a certain treatment [2,3]. Such an optimal balance has been described in evidence based clinical practice guidelines [2,3].

1.3 Clinical practice guidelines

In the late nineties Sackett and colleagues described that health care providers should provide evidence based practice: "the conscientious, explicit and judicious use of current best evidence in making decisions about the care of the individual patient" [32]. Thus, a physician practicing evidence based practice aims to enhance the best possible clinical outcomes for a patient, by integrating the following three components when making a clinical decision: a patient's choice and preferences, individual clinical expertise, and external evidence (e.g. available scientific evidence). This external evidence is often summarized in clinical practice guidelines, which comprise "systematically developed statements regarding a specific condition or field of medicine, and have been developed to assist practitioners in deciding on the appropriate healthcare resources that are required to improve a patient's condition" [33]. Clinical practice guidelines are effective in preventing overuse or underuse of healthcare resources and in reducing (unwarranted) practice variation [34]. External evidence in the form of clinical practice guidelines can never replace individual clinical expertise of the physician, but is meant to inform decision-making [32]. The individual physician still decides whether or not the external evidence applies to the patient's situation and preferences, and how the evidence should be integrated in the clinical decision. This, however, requires new skills of the physician, including the judgement and application of scientific evidence from clinical practice guidelines when deciding on a patient's treatment [32].

1.3.1 Clinical decision-making

Clinical decision-making refers to the cognitive process which is necessary to effectively assess and manage a patients' medical condition [35]. It plays a pivotal role in the management of NST-ACS patients. In Kahneman's interpretation of the dual process theory (i.e. two different kinds of thinking) two separate systems are used in decision-making, being the intuitive system (system I) and the analytical system (system II) [36,37]. A decision based on the intuitive system is generated rapidly and automatic, based on information that is already available and highly depends on previous gained experience of the decision maker. By contrast, decisions based on the analytical system are made much more deliberate, on the basis of actively gathered additional information and knowledge gained through learning. In clinical practice, both systems interact highly with each other. Often, clinical decision-making starts intuitively which generates several possible diagnoses. According to the theory, the analytic system is subsequently used to confirm or dismiss these possible diagnoses. Use of both these systems has been found important in decision-making as neglecting one of these has been associated with lower diagnostic accuracy [38]. However, in the case of NST-ACS, rapid treatment may be required and the use of both decision-making systems may be difficult. Especially the use of the analytic system, which requires more time. Therefore clinical practice guidelines have been developed which can guide physicians in evidence based decision-making.

1.3.2 Risk assessment

The European Society of Cardiology (ESC) and American Heart Association/American College of Cardiology (AHA/ACC) guidelines summarize all available scientific evidence regarding diagnosis, risk stratification, early pharmacological treatment, invasive procedures, and secondary prevention strategies in NST-ACS [2,3]. The guidelines can be used in selecting appropriate treatment for patients with NST-ACS. In deciding on the type of treatment, the guidelines recommend to determine the type of treatment on the basis of patients' risk for adverse cardiac events such as re-infarction or death. Patients at highest risk should be assigned to invasive therapies such as Primary Coronary Intervention (PCI) or Coronary Artery Bypass Grafting surgery (CABG), as they will benefit most from these treatments. Lower risk patients can be safely treated with pharmacological therapy [2,3]. This leaves the attending physician with the difficult and complex task to distinguish high risk patients from lower risk patients, by assimilating all relevant information from (among other) a patient's history, physical examination, and laboratory investigations. To assist physicians in assessing a patient's risk of adverse events, the use of risk stratification instruments have been recommended [2,3]. These risk instruments, i.e. cardiac risk scores, comprise of numerous established prognostic factors, including results from physical examination, electrocardiogram findings, cardiac blood makers and (non-)invasive imaging procedures, and provide the physician with a carefully weighed outcome.

Clinical judgement versus the use of clinical prediction models

Traditionally, physicians use their own clinical judgement, based on pre-gathered practice experience, knowledge and critical analysis, to decide on appropriate treatment in specific patient cases. In recent years however clinical prediction models have gained ground in medical decision-making. In the late eighties it was shown that a computer based prediction model was significantly more accurate in predicting survival rates in coronary artery disease than 49 cardiologists reviewing the same case summaries. Also, in contrast with cardiologists predictions, predictions of the computer based model did not vary for the same patient cases [39]. More recent studies recommend the use of clinical prediction models (cardiac risk scores) in addition to clinical assessment by the physician alone [40-42]. Although risk scores are rarely superior over clinical judgement, they have several advantages [3,43]. Provided that the scores are well-developed and extensively validated, they can weigh more factors simultaneously than a human brain can cognitively consider. Furthermore, they are more objective/reliable as they consistently give the same result on identical patient cases, whereas clinical judgment can be influenced by physician experience and can therefore result in unwarranted inconsistencies or variation i.e. with possible negative consequences for the patient's treatment [44].

In the management of NST-ACS, several validated cardiac risk scores have been developed over the years. The GRACE [45-47] and TIMI [48] risk scores are recommended by the ESC and ACC/AHA guidelines as they are most extensively validated in NST-ACS patient populations and have the highest discriminative ability [2,3]. Other risk scores concern the FRISC [49] and PURSUIT [50] risk score. A risk score is obtained by combining the clinical factors, presenting the outcome in low, intermediate or high risk categories. These scores are developed based on data derived from large clinical trials or registries. The validity of these instruments in terms of their ability to correctly predict the patient's risk of re-infarction or death during hospitalization or after discharge was reported to be good [49,51] (Table 1.1). In contrast to the other cardiac risk scores, in The Netherlands, the HEART score was developed to estimate a patient's risk of having chest pain with an underlying cardiac cause, and is used by several hospitals in the Netherlands [52,53].

Table 1.1 Characteristics of the different risk scoring instruments†

	Aim	Year of publication	Sample	Components‡	Discriminative ability
GRACE	Predicts in-hospital and 6 month death/ (re-)MI	2003, 2006	ACS patients N = 11,389	8 predictors: age, ST-segment deviation, elevated cardiac enzymes, Killip class∞, systolic blood pressure•, heart rate•, creatinine level, cardiac arrest•	Good
TIMI	Predicts in-hospital death	2000	ACS patients with UFH, N = 1957	6 predictors: age, ST-segment deviation, elevated cardiac enzymes, ≥1 risk factors for CAD, coronary stenosis ≥50%, angina events <24h	Moderate
FRISC	Predicts in-hospital death/ (re-)MI	2004	Unstable CAD N = 2457	7 predictors: age, ST-segment depression, elevated cardiac enzymes, previous MI, diabetes, gender, increased CRP	Good
HEART	Predicts MACE within 6 weeks	2008	Chest pain patients N = 122	5 predictors: age, ST-segment depression, elevated troponin levels, risk factors for CAD, medical history	Good

†The PURSUIT score is not presented in this table, because the instrument is outdated as it was developed before the availability of troponins, which now a days is an important prognosticator.
‡ Significant predictors for death and/or mortality ($p \leq 0.05$). ∞Severity of left ventricular damage. •At presentation in the hospital.
Abbreviations: ACS, acute coronary syndrome; ASA, aspirin; CAD, coronary artery disease; CRP, C-reactive protein, e.g. concentration of inflammation; MACE, major adverse cardiac event; re-MI, recurrent myocardial infarction; UFH, unfractionated heparin.

1.4 Suboptimal adherence

Although improving adherence to the ESC and ACC/AHA guidelines have been subject of numerous quality improvement programs that have been initiated over the years, large variations in treatment practices still exist [54-59]. Several studies found that not all NST-ACS patients receive care according to the guidelines, with patients at low risk of adverse cardiac events more likely to receive guideline recommended therapies than high risk patients [40,60-66]. A serious consequence of this treatment-risk paradox is the possible misuse of resources which can eventually harm patients i.e. unnecessary invasive treatments in low risk patients with a risk of treatment-related complications versus neglecting treatment in high risk patients who would benefit most from invasive treatment. Regarding this treatment risk paradox, the lack of routine application of cardiac risk scores in practice may be a possible explanation. In several studies a discrepancy between risk assessment by physicians' and risk assessment using validated risk scoring instruments was found. High risk patients were often not recognized, or the level of risk was underestimated by physicians when compared with calculated risk using a cardiac risk score [40-42,67]. Further, as mentioned before, physicians may have a skeptic attitude towards the use of risk scores in practice [4], and could possibly be one of several reasons that risk scores are not widely adopted in clinical practice [10,57,68,69].

1.4.1 Determinants influencing adherence

Physician's attitude towards the use of risk scores is a major factor for suboptimal use of these instruments in medical practice [4]. It has been mentioned before that physicians can (a) doubt the clinical sensibility of the risk score and rather base decisions on their own clinical judgement, (b) are concerned that certain important factors are not addressed by using the risk score, (c) have concerns on patient safety or fear legal risks, and (d) experience several practical issues, such as lack of availability of the risk score at the time of decision-making, user-unfriendliness, and a large number of models available [4,44,70].

Looking into guideline adherence in general, several factors on a guideline-, patient-, healthcare provider- and organizational level have been described in the literature before [70,71]. For instance on a guideline level, the complexity of the guideline or the scientific evidence base are identified as influential factors. On a patient level, clinical (e.g. high age) and non-clinical factors (insurance status) are distinguished. Healthcare provider-related factors include a lack of knowledge, lack of awareness or lack of motivation for change. On an organizational level, factors such as lack of time, staff and resources, or lack of management support are frequently mentioned. To develop and implement successful strategies initiatives in NST-ACS care, knowledge of underlying influential factors (i.e. barriers) of suboptimal adherence is necessary. Strategies to enhance guideline adherence are most successful when tailored to existing barriers [71]. Factors influencing the extent of adherence negatively are described in Table 1.2.

Table 1.2 Possible factors decreasing adherence to clinical guidelines

	Factor
Guideline	High complexity, i.e. difficult to use, requires specific resources
	Low trial-ability, i.e. extent to which a procedure can be experimented with
	Lack of relevance of the subject of the guidelines
	Lack of a clear scientific base
	Lack of adaptability (to local circumstances)
	Lack of local ownership, i.e. not developed in accordance with target group
	Lack of observability, i.e. degree to which clinical benefits are visible for its users
	Discordance between different guidelines
Patient	High age
	Co-morbidities
	Non-clinical factors (e.g. insurance status, patients' expectations and attitude)
	Patient's compliance to prescribed therapy
Healthcare provider	Lack of awareness
	Lack of familiarity
	Lack of self-efficacy, i.e. physician's believe that he/she cannot perform guideline recommendation
	Lack of outcome expectancy, i.e. physician's believe that performance of guideline recommendation will not lead to desired outcome
	Lack of agreement
	Lack of clear expectations
	Lack of knowledge
	Lack of motivation
	Lack of openness to innovations
	Concerns about legislation of guideline
	Physicians' characteristics: age, country, income, work-experience, training and job satisfaction
	Physician's habits/customs
	Reluctance to discharge patients on weekends
Organization	Lack of time, staff and resources
	High workload
	Lack of management support
	Financial disincentives
	Demanding regulation by accreditation of licensing bodies
	Social norms/belief of peers
	Influence of work environment (e.g. rural areas, day/ night shifts, close collaboration with other physicians)

1.5 Aims and research questions

It is unknown how often cardiac risk scores are actually used in practice. Just as which factors influence cardiac risk score use, and how physicians value the importance of cardiac risk scores in decision-making. This is, however, vital in understanding the potential underuse of risk scoring instruments. The studies in this thesis therefore aimed to:

1 Investigate the extent of guideline adherence in patients with Non-ST-Elevation Acute Coronary Syndrome, with a specific focus on the use of validated cardiac risk scoring instruments in practice.

What is the extent of guideline adherence in patients with NST-ACS?

2 Determine which factors on a patient-, healthcare provider- and organizational (i.e. hospital) level increase or decrease the extent of guideline adherence.

Which factors are associated with cardiac risk score use?

3 Provide insight in the process of decision-making regarding the management of Non-ST-Elevation Acute Coronary Syndrome.

What is the importance of various types of clinical information, including cardiac risk scores, in deciding on the management of patients with NST-ACS?

1.6 Outline of this thesis

Previous studies have focused on the extent of guideline adherence in the management of acute coronary syndrome patients, and indicated that there is an association between improved guideline adherence and reduced mortality rates. However, only a minority of studies made a clear distinction between the different sub-conditions of ACS, while NST-ACS concerns two heterogeneous conditions that ask for tailored treatment strategies as recommended by the guidelines. Also several studies suffered from methodological issues. In **chapter 2** we therefore aimed to provide a systematic overview of the literature regarding the extent of guideline adherence in treating NST-ACS patients, to identify guideline-practice gaps.

Cardiac risk scores seem underused in practice, despite being extensively validated in large studies, and being recommended by the guidelines. There is no insight into the extent to which cardiac risk scoring instruments are actually used and which factors influence this

use. This is the focus of **chapters 3 and 4**, where respectively the design and results of a cross-sectional multicentre study are described. By means of patient chart review, the extent of cardiac risk score use and associated factors was studied. Besides patient- or organization related factors, also, on a provider level, several factors might influence the use of risk scores. Therefore, in **chapter 5**, the implementation and use of cardiac risk scores is described from a physicians'/healthcare providers' perspective.

Risk assessment is a dynamic process. International cardiac guidelines recommend that physicians make use of multiple clinical factors (i.e. prognosticators) when deciding on the treatment of NST-ACS patients. However, there is little insight in how physicians' actually weigh different clinical information when deciding on the treatment of NST-ACS patients. In **chapter 6** the construct of patient scenario's (i.e. vignettes) and further details regarding the design of a clinical vignette study is described. The study was conducted to explore the importance of various types of clinical information in deciding on the management of patients with NST-ACS. In **chapter 7** the results of this clinical vignette study are presented.

In **chapter 8** an overall conclusion and interpretation of the results found in the preceding chapters are given. Further, methodological issues, and generalizability of the results are discussed. This chapter ends with implications for clinical practice and future research. In Table 1.3 an overview of the conducted studies that are part of this thesis are presented.

Table 1.3 Overview of conducted studies part of this thesis

Chapter	Design	Sample size	Outcome measures
2	Systematic review	NST-ACS patients 45 eligible articles	• Extent of guideline adherence in NST-ACS care; • Factors influencing the extent of adherence; • Impact of guideline adherence on patient outcomes (death/myocardial infarction).
3	Detailed study protocol of a cross-sectional multicentre Study	Not applicable	Not applicable
4	Patient chart review study	13 hospitals, n = 1788 NST-ACS patients	• Extent of cardiac risk score use in clinical practice; • Factors influencing cardiac risk score use.
5	Qualitative study; semi-structured interviews	11 hospitals, n = 31 health care providers	• Motivation for implementing cardiac risk score use (context); • Process of implementing cardiac risk scores (process); • Perceptions of healthcare providers towards the use of cardiac risk scores in practice (content).
6	Description of construction of clinical vignettes and detailed study protocol	Not applicable	Not applicable
7	Cross-sectional survey study, containing clinical vignettes describing patients scenarios	n = 129 cardiologists	• Relative importance of different clinical factors in deciding on performing coronary angiography; • Impact of risk score information on cardiologists' decision-making.

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2

Guideline adherence in NST-ACS: a systematic review

Adherence to cardiac practice guidelines in the management of Non ST-Elevation Acute Coronary Syndromes: a systematic literature review

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Abstract

Background

In the management of non-ST-elevation acute coronary syndrome (NST-ACS) a gap between guideline-recommended care and actual practice has been reported. A systematic overview of the actual extent of this gap, its potential impact on patient-outcomes, and influential factors is lacking.

Objective

To examine the extent of guideline adherence, to study associations with the occurrence of adverse cardiac events, and to identify factors associated with guideline adherence.

Method

Systematic literature review, for which PUBMED, EMBASE, CINAHL, and the Cochrane library were searched until March 2016. Further, a manual search was performed using reference lists of included studies. Two reviewers independently performed quality-assessment and data extraction of the eligible studies.

Results

Adherence rates varied widely within and between 45 eligible studies, ranging from less than 5.0 % to more than 95.0 % for recommendations on acute and discharge pharmacological treatment, 34.3 % - 93.0 % for risk stratification, and 16.0 % - 95.8 % for performing coronary angiography. Seven studies indicated that higher adherence rates were associated with lower mortality. Several patient-related (e.g. age, gender, co-morbidities) and organization-related (e.g. teaching hospital) factors influencing adherence were identified.

Conclusion

This review showed wide variation in guideline adherence, with a substantial proportion of NST-ACS patients possibly not receiving guideline-recommended care. Consequently, lower adherence might be associated with a higher risk for poor prognosis. Future research should further investigate the complex nature of guideline adherence in NST-ACS, its impact on clinical care, and factors influencing adherence. This knowledge is essential to optimize clinical management of NST-ACS patients and could guide future quality improvement initiatives.

2.1 Background

Non-ST-Elevation Acute Coronary Syndromes (NST-ACS) comprise one of the most common types of ACS, encompassing the two sub-conditions Unstable Angina (UA) and Non-ST-Elevation Myocardial Infarction (NSTEMI). The proportion of patients diagnosed with these conditions has increased substantially in the past two decades, whereas the proportion of ST-Elevation Myocardial Infarction (STEMI) patients has decreased [1]. In addition, NST-ACS patients have a higher long-term risk of myocardial infarction and/or death as compared with STEMI patients [2-5]. In the management of NST-ACS clinical practice guidelines (CPG's) have become increasingly important. CPG's are developed to guide physicians in clinical decision-making and to decrease variability in treatment practices in order to enhance the quality of care [6-8]. For the management of NST-ACS, several guidelines exists, such as the National Institute for Health and Care Excellence (NICE) guidelines[9], the European Society of Cardiology (ESC) guidelines [10], and the American College of Cardiology/ American Heart Association (ACC/AHA) guidelines [11]. The ESC and ACC/AHA are most known and comprise class I recommendations on acute in-hospital pharmacological treatment, risk stratification, performing coronary angiography (CA), and the prescription of discharge medications [10,11]. A gap between evidence-based medicine incorporated in these guidelines and actual practice seems to exist, with various studies indicating that a substantial proportion of NST-ACS patients does not receive care according to the guidelines [12,13]. Up until now, only two literature reviews reported on potential guideline-practice gaps in the management of ACS patients. One review summarized literature on guideline adherence in ACS patients in general [14], whereas the second focused on adherence in the management of NST-ACS patients specifically [15]. This latter review, however, only included studies from a single registry (i.e., CRUSADE) conducted primarily in the USA. In addition, previous research concluded that the extent of adherence to clinical guidelines can be influenced by factors related to the patient, the health care provider or the organization [16-18]. Several studies showed a wide variety of factors that were associated with (under) utilization of evidence-based therapies, but an overview of potential factors associated with guideline adherence in NST-ACS patients is lacking. Given that in a previous study low guideline adherence in NST-ACS patients was associated with adverse cardiac events, such as death and myocardial infarction (MI) [19], and NST-ACS prevalence rates are increasing [20], insight in the extent of guideline adherence, potential practice gaps and the impact on patient outcomes in this specific patient group is necessary. The results can be used to stress the importance of optimizing clinical management among policy-makers and clinicians. The aims of the current systematic literature review were to 1) examine the extent of adherence to international cardiac guideline recommendations, 2) study the association between guideline adherence and adverse cardiac events (i.e., death and/or MI), and 3) identify potential factors associated with guideline adherence in the management of patients with NST-ACS.

2.2 Methods

A systematic review of the literature was conducted. In reporting the results of this study, the "Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)" statement was used [21].

2.2.1 Search strategy

A literature search was conducted in PUBMED (including MEDLINE), EMBASE, CINAHL, and the Cochrane library until March 2016. The search strategies were constructed in cooperation with an information specialist from the library of the VU University Amsterdam and included search terms related to adherence combined with terms related to guidelines or protocols, MI, and UA (Appendix A). No restrictions were applied. In addition to the electronic search, reference lists of the included studies were manually screened for additional relevant articles. When the full-text of a study was not available online, either the first author was approached to request a copy of the study or a full-text copy was ordered online. The Cochrane database for *systematic* reviews was searched for systematic literature reviews on adherence in NST-ACS care, but none were found.

2.2.2 Selection of studies

Two reviewers (JE, ND) independently screened all studies identified in the initial search on title and abstract. Studies were selected for full-text screening if guideline adherence in NST-ACS patients was addressed in either the title or abstract. In case of disagreement between the reviewers, a third reviewer was consulted (IvdW). Subsequently, two reviewers (JE, ND) screened the full-text of these selected studies independently. Studies that met all of the following criteria were included in this systematic literature review:

a) The study focused on adherence in NST-ACS patients to either the American College of Cardiology (ACC/AHA) or the European Society of Cardiology (ESC) guidelines (versions developed since 2000);
b) The study reported on one or more of the following guideline recommendations: acute in-hospital pharmacological treatment, risk stratification to decide on the need for early invasive procedures (i.e. electrocardiogram (ECG), troponin assessment, or use of validated risk scores), performance of in-hospital CA in intermediate to high risk patients, and/or the prescription of discharge medications (Box 2.1);
c) The study sample included adults (≥18 years) with NST-ACS (i.e., UA and/or NSTEMI);
d) The study design was observational or (quasi-) experimental;
e) The study was conducted in a hospital setting.

Box 2.1 Trends in class of evidence of guideline recommendations in NST-ACS patients

Cardiac guideline recommendations †‡	**ESC**				**ACC/AHA**			
Year of publication	***2015***	***2011***	***2007***	***2002∞/ 2000***	***2014***	***2011∞***	***2007***	***2002∞/ 2000***
Acute (<24 h) in-hospital pharmacological treatment								
• Prescription of aspirin	IA	IA	IA	IA	IA	IA	IA	IA
• Prescription of beta-blockers	IB	IB	IB	IB	IA	-	IB	IB
• Prescription of platelet aggregation inhibitors ϕ	IA	IA	IA	IB	IB	IB	IA	IB
• Prescription of glycoprotein IIb/IIIa inhibitors	IIb-A	IB	IB	IA	IIb-B	IB	IB	IA
• Prescription of anti-coagulant (e.g. heparin)	IB	IA	IA	IA	IA/IB	IA	IA/IB	IA
Risk stratification								
• ECG within 10 min after arrival in the hospital	IB	IB	IC	-	IC	-	IB	IC
• Troponin assessment	IA	IA	IA	IA	IA	-	IB	IB
• (Use of) validated risk scores for prognosis (e.g. GRACE)	IB	IB	IB	-	IA	-	IIa-B	-
Invasive procedure in intermediate to high risk patients								
• (Early) In-hospital coronary angiography (CA)	IA	IA	IA	IB	IA	IA	IA	IA
Discharge medications								
• Prescription of ACE inhibitor and/or ARB	IA	IA	IA	-	IA	-	IA	IA
• Prescription of aspirin	IA	IA	IA	IA	IA	IA	IA	IA
• Prescription of beta-blockers	IA	IA	IA	IA	IC	-	IB	IB
• Prescription of platelet aggregation inhibitors ϕ	IA	IA	IA	IB	IB	IB	IB	IB
• Prescription of statins	IA	IB	IB	-	IA	-	IA	IA

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II AT1 receptor blockers; CA, coronary angiography; ECG, electrocardiogram; GRACE, global registry of acute coronary events.
†class of recommendation: class I refers to the condition in which there is evidence or general agreement that a certain procedure or treatment is beneficial, useful, effective, and thus recommended/should be performed; class II refers to the condition in which there is conflicting evidence about the usefulness or efficacy of a certain procedure or treatment, and thus should (class IIa) or may (class IIb) be considered. class III refers to the condition in which there is evidence or general agreement that a certain procedure or treatment is not useful or effective, and even in some cases be harmful, and is thus not recommended.
†Level of evidence: Level A refers to data derived from multiple randomized clinical trials or meta-analyses; Level B refers to data derived from a single randomized clinical trial or large non-randomized studies; Level C refers to consensus of opinion of the experts and/or small studies, retrospective studies or registries.
‡In eligible patients according to the guidelines. ∞ Guideline update. ϕ e.g. thienopyridine.

Studies were excluded from this systematic literature review when:

a) Adherence to ACC/AHA and/or ESC guideline recommendations was studied in a subgroup of NST-ACS patients (e.g. NST-ACS patients with diabetes mellitus;
b) The study design was not observational or (quasi-) experimental (e.g., review, editorial, letter to the editor, opinion paper, conference abstract, qualitative study, or design article).

2.2.3 Methodological quality assessments

The methodological quality of the included studies was assessed by two reviewers independently (JE, ND), using a checklist based on the STROBE statement for observational studies [22]. The checklist comprised 11 items: title and abstract, introduction and objectives, study design, participant selection and sample size, variables, data sources and methods, data analyses, participant flow, descriptive data, main results, and discussion. Each item on the checklist was scored 0 in case an adequate description of the item in the paper was lacking or not reported, 0.5 in case an adequate description was given but minimal data were reported, or 1 in case both were adequate. Scores on the 11 items were summed and as a result, each study received a total score that ranged from 0 (poor study quality) to 11 (excellent study quality). Scores between 0-6 reflected poor study quality, scores >6 – <8 reflected moderate study quality, scores ≥8 – <10 reflected good study quality and scores ≥10 reflected excellent study quality. Agreement between the reviewers was considered substantial: in 87 % of the assessed studies quality scores of both reviewers did not differ more than 0.5 point and there were no studies of which the scores of both reviewers differed more than one point.

2.2.4 Data extraction

Data of the included studies were extracted by one reviewer (JE) and thoroughly checked by a second reviewer (ND). Using a standardized data extraction form, the following characteristics were extracted: first author, year of publication, country of data collection, study design, data collection methods, study sample, type of guideline(s) evaluated (i.e., ACC/AHA and/or ESC), type of recommendation(s) evaluated, and main results. In the data extraction process, the following criteria were applied:

- When included studies focused on the management of both STEMI and NST-ACS patients, only the results for NST-ACS patients were extracted;
- When data of the included studies were collected at different time points (e.g., cohort studies), only details of the latest measurement were reported as these provided the most recent information;
- When studies had a pretest-posttest design in which the effect of an intervention was assessed, only details from the pretest measurement were extracted, as we did not aim to evaluate intervention effects;
- Of the studies focusing on potential factors associated with guideline adherence, only the statistically significant associations from multivariable analyses were extracted ($p \leq 0.05$).

2.3 Results

2.3.1 Description of the studies

The final selection of studies consisted of 45 studies (Figure 2.1). Of the included studies, 21 studies were conducted in the USA [12,13,19,23-40], 12 in Europe [41-52], four in Canada [53-56], five in Asia [57-61], two in New-Zealand [62,63], and one study was conducted in multiple countries [64]. The majority of studies had an observational study design, with the exception of three studies who respectively concerned a pilot study [52], a descriptive study [61], and a before-after study [47]. Sample sizes of the included studies ranged from 121 to 2,515,106 patient admissions. Two studies were single-centre studies [58,63], while the other studies were multicentre studies.

2.3.2 Methodological quality

The methodological quality assessment indicated that the quality of 36 included studies was excellent or good [12,13,19,23-25,27-38,40,41,44,45,47,48,50-60,64], whereas the quality of seven studies was scored moderate [26,42,46,49,61,62,63] and two studies were scored poor [39,43] (Table 2.1). Most studies lacked a detailed description of primary and secondary outcomes and related measurement sources, the handling of missing data, and/or the adjustment for confounders in multivariable analyses. With regard to the description of the study design, the majority of studies referred to a previously reported design paper.

2.3.3 Main results

Results were categorized into (1) the extent of adherence to ACC/AHA and/or ESC guideline recommendations; (2) the association between guideline adherence and adverse cardiac events (i.e., death and/or MI); and/or (3) potential factors associated with guideline adherence. Given that guideline recommendations were overall comparable, in this categorization no distinction between the ACC/AHA and ESC guidelines was made. Also different versions of both guidelines, published over the years, were highly comparable in class and level of evidence (Box 2.1).

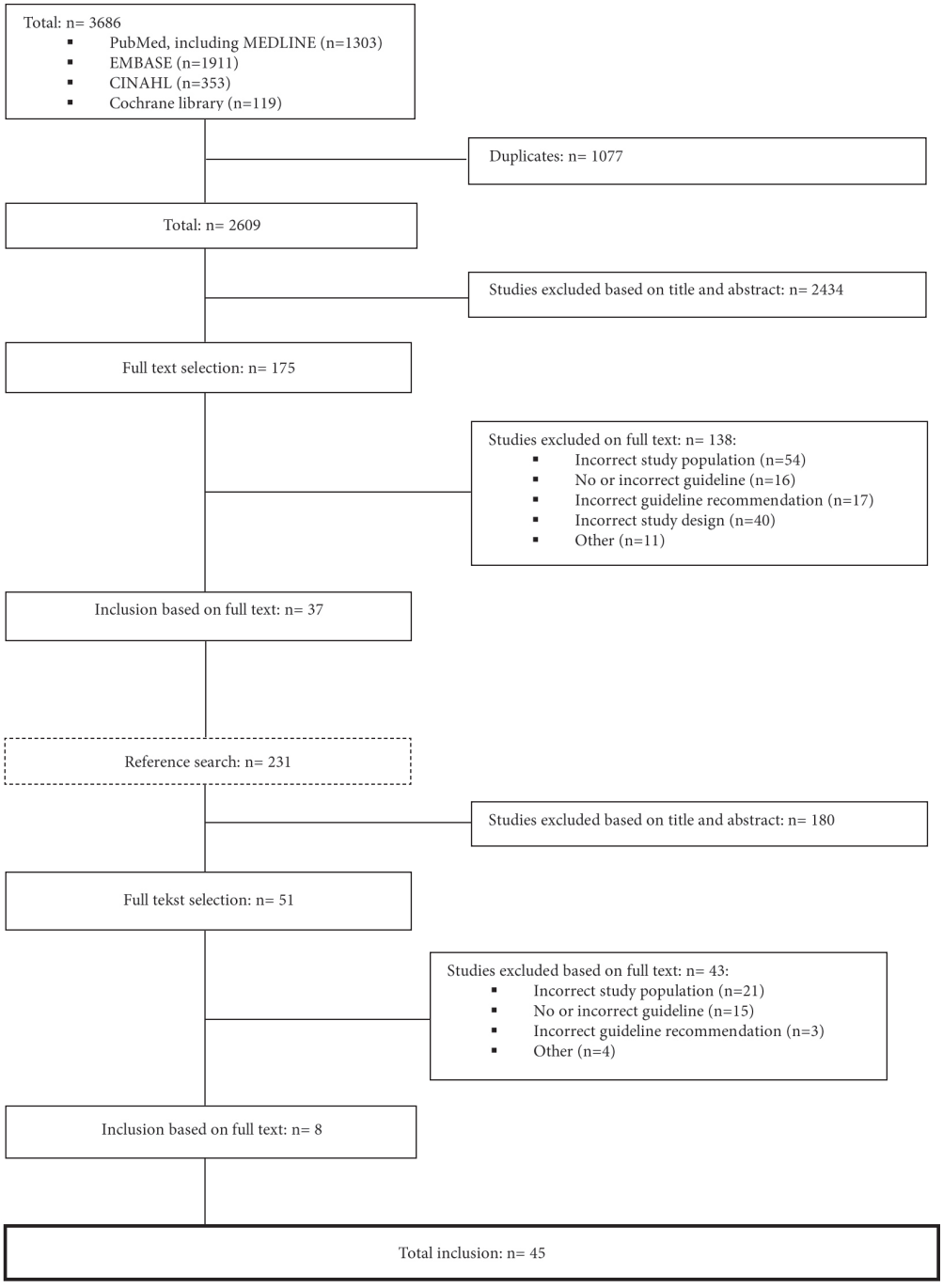


Figure 2.1 Flow chart of article selection

Table 2.1 Methodological quality of the included studies based on the STROBE criteria

Reference	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
Total score	9	10	9.5	10.5	8.5	7.5	10	9	6.5	10.5	7	9.5	10	9.5	9
Reference	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**
Total score	8	10	10	7	10	9	5.5	10	10	9.5	9.5	10	8	10	9
Reference	**31**	**32**	**33**	**34**	**35**	**36**	**37**	**38**	**39**	**40**	**41**	**42**	**43**	**44**	**45**
Total score	9	9	8	9	8.5	6.5	10	9.5	7	6	8	7.5	9	9.5	9

Methodological quality was assessed using a checklist based on the STROBE criteria, consisting of 11 items. Items were scored as following: 1 = described, ½ = partly described, 0 = not/insufficiently described. Total score ranged from 0-11, where scores between 0 - 6 reflected poor study quality, >6 - <8 moderate study quality, ≥8 - <10 good study quality and ≥10 excellent study quality.
1.Amsterdam et al. 2009, 2. Banihashemi et al. 2009, 3. Bhatt et al. 2004, 4. Chandra et al. 2009, 5. Cheng et al. 2010, 6. Diercks et al. 2006, 7. Diercks et al. 2007, 8. Dziewierz et al. 2007, 9. Ellis et al. 2004, 10. Engel et al. 2015, 11. Ferreira et al. 2004, 12. Goldberg et al. 2007, 13. Hoekstra et al. 2005, 14. Kassab et al. 2013, 15. Kassaian et al. 2015, 16. Lee et al. 2008, 17. Maddox et al. 2012, 18. Maier et al. 2008, 19. Mandelzweig et al. 2006, 20. Mehta et al. 2006, 21. Miller et al. 2007, 22. Nieuwlaat et al. 2004, 23. Olivari et al. 2012, 24. Peterson et al. 2003, 25. Peterson et al. 2006, 26. Peterson et al. 2008, 27. Polonski et al. 2007, 28. Rao et al. 2009, 29. Roe, Parsons, et al. 2005, 30. Roe, Peterson, et al. 2005, 31. Roe, Chen, et al. 2006, 32. Roe, Peterson, et al. 2006, 33. Roe et al. 2007, 34. Schiele et al. 2005, 35. Sherwood et al. 2014, 36. Sinon et al. 2014, 37. Somma et al. 2012, 38. Sonel et al. 2005, 39. Tang et al. 2005, 40. Tricoci et al. 2006, 41. Valli et al. 2014, 42. Vikman et al. 2003, 43. Yan et al. 2007, 44. Zeymer et al. 2014, 45. Zhang et al. 2009.

The extent of adherence to cardiac guideline recommendations

Acute in-hospital pharmacological treatment

Thirty-four studies reported on the extent of adherence to guideline recommendations on acute in-hospital pharmacological treatment, including the prescription of aspirin, beta-blockers, platelet aggregation inhibitors (e.g., clopidogrel), glycoprotein IIb/IIIa inhibitors, and/or heparin [12,13,19,23,25,26,28,29,31-38,40-46,48,49,51-54,59-63]. Overall, adherence rates in these studies varied from 0.5% [61] to 98.3% [60]. The three lowest adherence rates were related to recommendations regarding the early prescription of glycoprotein IIb/IIIa inhibitors (0.5 % [61], 0.6 % [62] , and 1.8 % [59], whereas the three highest adherence rates were related to recommendations on the early prescription of aspirin (97.0 % [41], 97.1 % [13], and 98.3% [60]) (Table 2.2).

Risk stratification

Six studies reported on guideline adherence regarding risk stratification to decide on the need for early invasive procedures [25,27,43,47,50,61]. Adherence rates of 34.3 % [27], 35.6 % [25], and 82.0 % [47] for the performance of an ECG within 10 min after arrival at the hospital were reported. In addition, two studies, one with poor and another with moderate methodological quality, indicated that in respectively 92.0 % and 93.0 % of NST-ACS patients

troponin assessment was used as a risk stratification method [43,61]. One study reported on the use of validated risk-scoring instruments in practice, such as the Global Registry of Acute Coronary Events (GRACE) or the Thrombolysis In Myocardial Infarction (TIMI) risk scores. In 57% of NST-ACS patients a validated risk score outcome was documented in their medical chart, with scores ranging between hospitals from 16.7 % to 87.0 % [50].

Performing in-hospital CA

Twenty-four studies reported on adherence to guideline recommendations on the performance of in-hospital CA in intermediate to high-risk patients [24-27,31,33-39,42-44,46,48,49,51,55,56,60,62,63]. Overall, CA was performed in 16.0 % [62] to 95.8 % [51] of NST-ACS patients. More specifically, in 22.7 % [27] to 47.5 % [25] of patients in-hospital CA was performed within 24 h after admission, whereas in 42.5 % [34] to 65.8 % [25] CA was performed in-hospital within 48 h after admission. In four studies CA-adherence rates were stratified by patients' risk status, with results being mixed. In three of these studies high-risk patients were less likely to receive in-hospital CA as compared with low-risk patients [38,55,56], while in one study 25.0 % of low-risk patients received in-hospital CA versus 56.0 % of high-risk patients [43] (Table 2.3). However, methodological quality of this latter study was scored poor (Table 2.1).

Discharge medications

Twenty-three studies reported on guideline adherence with regard to recommended discharge medications, including angiotensin-converting-enzyme (ACE) inhibitors /angiotensin II AT1 receptor blockers (ARBs), aspirin, beta-blockers, platelet aggregation inhibitors (e.g., clopidogrel), and/or statins [12,13,19,23,26,30,31,33,34,36,38,40-44,46,49,51,57,58,62,64]. Overall, adherence rates in these studies varied from 4.2 % [58] to 97.3 % [13]. The three lowest adherence rates were related to recommendations regarding the prescription of ARBs (4.2 %) [58], clopidogrel (9.5 % for NSTEMI and 5.1 % for UA) [62], and aspirin (16.0 %) [57] at discharge. Hence, all three studies had relatively small sample sizes (ranging from 380-1,331). Although in the majority of studies low adherence rates were reported for the prescription of clopidogrel at discharge (<59.0 %), in six studies adherence rates were found ranging from 67.0 % to 90.8 % [13,23,31,40,51,58]. The study with the highest adherence score, however, concerned a single center study with a small sample size (n=380). The three highest adherence rates were related to recommendations regarding the prescription of aspirin (96.0 % [41] and 97.3 % [13], respectively) and beta-blockers (97.0 % [13]) at discharge. Overall, adherence rates for the prescription of aspirin at discharge were higher than 90.0 %, but in one study only 16.0 % of NST-ACS patients were prescribed this type of medication at discharge [57]. However, combined with the administration of clopidogrel 61.8 % also received aspirin (Table 2.2).

Table 2.2 Characteristics of studies on the extent of adherence to pharmacological therapies recommended by the ACC/AHA and/or ESC NST-ACS guidelines

First author, year *(country)* [PMID]	Study design	Sample	Main results *I = acute pharmacological care (<24 h after admission)* *II = discharge medications*
Amsterdam, 2009 [23] (*USA*) [PMID: 1985369]	Prospective, multi-center, observational registry (CRUSADE) †	138,714 NST-ACS patients, enrolled from 547 hospitals	**I.** aspirin 96.0 %, BB 90.8 %, clopidogrel 57.8 %, GP IIb/IIIa inhibitors 47.2 %, any heparin 87.1 % **II.** ACE/ARB 69.4 %, aspirin 94.7 %, BB 92.4 %, clopidogrel 73.6 %, statin 88.8 % *(Based on last measurement 2005, n=138.714 NSTEMI patients)*
Banihashemi, 2009 [53] (Canada) [PMID: 19958875]	Prospective, multi-center, observational registry (GRACE) †	5,806 NST-ACS patients, enrolled from 53 hospitals	**I.** Overall, 67.1 % of patients received clopidogrel and/or GP IIb/IIIa inhibitors ≤ 24h: 97.8 % of these patients received clopidogrel, 2.2 % received GP IIb/IIIa inhibitors.
Chandra, 2009 [25] (*USA*) [PMID: 19282062]	Prospective, multi-center, observational registry (CRUSADE) †	33,238 NST-ACS patients, enrolled from 344 hospitals	**I.** aspirin 96.0 %, BB 90.9 %, clopidogrel 56.2 %, GP IIb/IIIa inhibitor 48.0 %, any heparin 88.2 %
Cheng, 2010 [57] (*Taiwan*) [PMID: 20552592]	Prospective, multi-center, observational registry (T-ACCORD)	1,331 NST-ACS patients, enrolled from 27 hospitals	**II.** ACE or ARB 60.0 %, aspirin only 16.0 %, clopidogrel only 17.3 %, aspirin and clopidogrel 61.8 %, BB 50.2 %, statin 68.8 %
Diercks, 2006 [26] (*USA*) [PMID: 16824844]	Prospective, multi-center, observational registry (CRUSADE) †	80,845 NST-ACS patients (Number of hospitals unknown)	**I.** aspirin 92.2 %, BB 80.1 %, clopidogrel 41.3 %, GP IIb/IIIa inhibitor 37.9 %, any heparin 84.3 % **II.** ACE/ARB 56.9 %, aspirin 90.4 %, BB 84.3 %, clopidogrel 56.1 %, statin 68.1 %
Dziewierz, 2007 [45] (*Poland*) [PMID: 17496494]	Prospective, multi-center, observational registry (Malopolska registry of ACS)	807 NSTEMI patients, enrolled from 29 hospitals	**I.** mean pharmacotherapy index: 4.3 (range 0-7, one point for each medication received, including ACE/ARB, aspirin, BB, clopidogrel, GP IIb/IIIa inhibitor, LMW Heparin, and statin). Per medicine: ACE/ARB 76.6 %, aspirin 94.9 %, BB 83 %, clopidogrel 9.9 %, GP IIb/IIIa inhibitor 2.9 %, LMW Heparin 73.9 %, statin 84.4 %
Ellis, 2004 [62] (*New Zealand*) [PMID: 15326506]	Prospective, multi-center, observational audit	930 ACS patients, of which 333 UA and 287 NSTEMI, enrolled from 36 hospitals	**I.** aspirin 79.0 % NSTEMI / 81.0 % UA, clopidogrel 13.0 % NSTEMI / 6.2 % UA, GP IIb/IIIa inhibitor 2.8 % NSTEMI / 0.6 % UA, LMW heparin 64.0 % NSTEMI / 51.0 % UA, UF heparin 8.8 % NSTEMI / 6.6 % UA **II.** ACE 45.0 % NSTEMI / 39.0 % UA, aspirin 83.0 % NSTEMI / 80.0 % UA, BB 63.0 % NSTEMI / 59.0 % UA, clopidogrel 9.5 % NSTEMI / 5.1 % UA, statin 55.0 % NSTEMI / 52.0 %UA
Ferreira, 2004 [46] (*Portugal*) [PMID: 15641292]	Prospective, multi-center, observational registry (National Registry of ACS)	7,348 ACS patients, of which 2,858 NSTEMI and 1,154 UA, enrolled from 44 hospitals	**I.** aspirin 96.0 % NSTEMI / 96.0 % UA, BB 67.0 % NSTEMI / 76.0 % UA, GP IIb/IIIa inhibitor 37.0 % NSTEMI / 26.0 % UA, any heparin 97.0 % NSTEMI / 95.0 % UA **II.** ACE 66.0 % NSTEMI / 53.0 % UA, aspirin 91.0 % NSTEMI / 91.0 % UA, BB 64.0 % NSTEMI / 71.0 % UA, statins 77.0 % NSTEMI / 78.0 % UA

Abbreviations: ACE, angiotensin-converting-enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensin II AT1 receptor blocker; BB, beta-blocker; CRUSADE, Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines; GP IIb/IIIa, Glycoprotein IIb/IIIa receptor inhibitors; GRACE, Global Registry of Acute Coronary Events; LMW, low molecular weight; NST-ACS, non-ST-elevation acute coronary syndrome; NSTEMI, non-ST-elevation myocardial infarction, PMID, PubMed ID; T-ACCORD, The Action to Control Cardiovascular Risk in Diabetes; UA, unstable angina; UF, unfractioned. †Concern large registries that provide access to quality improvement tools, e.g. quarterly feedback reports/benchmarks.

Table 2.2 Characteristics of studies on the extent of adherence to pharmacological therapies recommended by the ACC/AHA and/or ESC NST-ACS guidelines (continued)

First author, year *(country)* [PMID]	**Study design**	**Sample**	**Main results** *I = acute pharmacological care (<24 h after admission) II = discharge medications*
Goldberg, 2007 [64] (*14 countries in North and South America, Europe, Australia and New- Zealand*) [PMID:17846396]	Prospective, multi-center, observational registry (GRACE) †	26,413 ACS patients, of which 12,444 NSTEMI, enrolled from 113 hospitals	**II.** ACE 73.0 %, aspirin 95.0 %, BB 90.0 %, statin 83.0 % *(Based on latest measurement in 2005)*
Hoekstra, 2005 [28] (*USA*) [PMID: 15863399]	Prospective, multi-center, observational registry (CRUSADE) †	56,804 NST-ACS patients, enrolled from 443 hospitals	**I.** GP IIb/IIIa inhibitors were provided in 35.5 % of patients
Kassab, 2013 [58] (*Malaysia*) [PMID: 22845427]	Retrospective, cross-sectional, single center study	380 ACS patients, of which 215 UA and 76 NSTEMI, enrolled from 1 hospital	**II.** ACE 69.7 % NSTEMI / 60.5 % UA, ARB 7.9 % NSTEMI / 4.2 % UA, aspirin 92.1 % NSTEMI / 85.6 % UA, BB 82.9 % NSTEMI / 81.4 % UA, clopidogrel 90.8 % NSTEMI / 78.6 % UA, statin 94.7 % NSTEMI / 94.0 % UA
Kassaian, 2015 [60] (*Iran*) [26671947]	Prospective, multi-center, observational registry	1226 NST-ACS patients, enrolled from 11 hospitals	**I.** aspirin 98.3 %, BB 88.7 %, clopidogrel 89.7 %, any heparin 93.9 %
Maddox, 2012 [30] (*USA*) [PMID: 22570355]	Prospective, multi-center, observational registry (GWTG-CAD) †	23,186 NSTEMI patients, enrolled from 382 hospitals	**II.** 53.9 % had clopidogrel prescribed at discharge.
Maier, 2008 [41] (*Germany*) [PMID: 18061689]	Prospective, multi-center observational registry (BMIR)	6,080 ACS patients, of which 1,766 NSTEMI, enrolled from 22 hospitals	**I.** aspirin 97.0 %, BB 90.8 %, GP IIb/IIIa inhibitors 43.7 % **II.** ACE 80.5 %, aspirin 96 %, BB 93.6 %, statins 84.1 % *(Based on last measurement 2004, n=1087 NSTEMI patients)*
Mandelzweig, 2006 [42] (*32 countries in Europe and Mediterranean basin*) [PMID: 16908490]	Prospective, multi-center, observational survey (EHS-ACS-II)	6,358 ACS patients, of which 3,063 NST-ACS, enrolled from 190 hospitals	**I.** aspirin 94.5 %, BB 82.8 %, clopidogrel 67.4 %, GP IIb/IIIa 20.8 %, any heparin 90.0 % **II.** ACE or ARB 67.0 %, BB 78.0 %, aspirin 88.0 %, clopidogrel or other 59.0 %, statins 76.0 %
Mehta, 2006 [31] (*USA*) [PMID: 17030838]	Prospective, multi-center, observational registry (CRUSADE) †	113,595 NST-ACS patients, enrolled from 434 hospitals	**I.** aspirin 95.3 %, BB 86.8 %, clopidogrel 51.5 %, GP IIb/IIIa inhibitor 44.6 %, any heparin 87.4 % **II.** ACE 63.7 %, aspirin 93.2 %, BB 88.6 %, clopidogrel 68.7 %, statin 86.8 % *(Based on last quarter measurement n=11.111)*
Miller, 2007 [29] (*USA*) [PMID: 17679127]	Prospective, multi-center, observational registry (CRUSADE) †	72,054 NST-ACS patients, enrolled from 509 hospitals	**I.** 82.5 % of patients received beta blockers

Abbreviations: ACE, angiotensin-converting-enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensin II AT1 receptor blocker; BB, beta-blocker; BMIR, Berlin Myocardial Infarction Registry; CRUSADE, Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines; EHS-ACS-II, Second Euro Heart Survey on Acute Coronary Syndrome; GP IIb/IIIa, Glycoprotein IIb/IIIa receptor inhibitors; GRACE, Global Registry of Acute Coronary Events; GWTG-CAD, Get With the Guidelines - Coronary Artery Disease; NST-ACS, non-ST-elevation acute coronary syndrome; NSTEMI, non-ST-elevation myocardial infarction; NRMI, National Registry of Myocardial Infarction; PMID, PubMed ID; UA, unstable angina. †Concern large registries that provide access to quality improvement tools, e.g. quarterly feedback reports/benchmarks

Table 2.2 Characteristics of studies on the extent of adherence to pharmacological therapies recommended by the ACC/AHA and/or ESC NST-ACS guidelines (continued)

First author, year *(country)* [PMID]	**Study design**	Sample	**Main results** *I = acute pharmacological care (<24 h after admission) II = discharge medications*
Nieuwlaat, 2004 [43] (*The Netherlands*) [PMID: 15497784]	Prospective, multi-center, observational survey	421 ACS patients, of which 198 NST-ACS, enrolled from 6 hospitals.	**I.** aspirin 91.0 %, BB 81.0 %, clopidogrel 25.0 %, any heparin 89.0 % **II.** ACE 36.0 %, aspirin 84.0 %, BB 79.0 %, clopidogrel 25.0 %, statin 69.0 %
Peterson, 2003 [32] (*USA*) [PMID: 12849658]	Prospective, multi-center, observational registry (NRMI) †	60,770 NSTEM patients, enrolled from 1189 hospitals	**I.** 25.0% of patients received GP IIb/IIIa inhibitors
Peterson, 2006 [19] (*USA*) [PMID: 16639050]	Prospective, multi-center, observational registry (CRUSADE) †	64,775 NST-ACS patients, enrolled from 350 hospitals	Overall adherence rate: 74.0 % (range 63.0 % for lowest quartile to 82.0 % for highest quartile) **I.** aspirin 92.0 %, BB 79.0 %, clopidogrel 41.0 %, GP IIb/IIIa inhibitor 36.0 %, any heparin 82.0 % **II.** ACE 61.0 %, aspirin 90.0 %, BB 84.0 %, clopidogrel 54.0 %, statin 76.0 %
Peterson, 2008 [33] (*USA*) [PMID: 19032998]	Prospective, multi-center, observational registry (NRMI) †	2,515,106 ACS patients, of which 1,368,497 NSTEMI, enrolled from 2157 hospitals	**I.** aspirin 88.0 %, BB 79.0 %, any heparin 74.0 % **II.** ACE/ARB 65.0 %, aspirin 90.0 %, BB 88.0 %, statin 82.0 % *(Based on data last cohort 2003-2006, n=227.845 NSTEMI patients)*
Polonski, 2007 [44] (*Poland*) [PMID: 17853315]	Prospective, multi-center observational registry (Polish registry of ACS)	100,193 ACS patients, of which ±42,281 UA and ±26,651 NSTEMI, enrolled from 417 hospitals	**I.** aspirin 92.0 % NSTEMI / 92.0 % UA, BB 78.0 % NSTEMI, 82.0 % UA, thienopyridine 42.0 % NSTEMI / 36.0 % UA, any heparin 76.0 % NSTEMI / 65.0 % UA **II.** ACE 75.0 % NSTEMI / 76.0 % UA, aspirin 85.0 % NSTEMI / 86.0 % UA, BB 77.0 % NSTEMI / 80.0 % UA, thienopyridine 38.0 % NSTEMI / 30.0 % UA, statins 81.0 % NSTEMI / 82.0 % UA
Rao, 2009 [54] (*Canada*) [PMID: 19332190]	Prospective, multi-center, observational registries (GRACE) †	11,177 ACS patients, of which 5,194 NSTEMI and 2,892 UA, enrolled from 53 hospitals	**I.** Clopidogrel 73.6 % NSTEMI / 64.6 % UA *(Based on latest measurement in 2007, n=3063 NST-ACS)*
Roe, 2005 [37] (*USA*) [PMID: 16157831]	Prospective, multi-center, observational registry (CRUSADE) †	23,298 NST-ACS patients (number of hospitals unknown)	**I.** aspirin 90.8 %, BB 76.9 %, clopidogrel 37.8 %, GP IIb/IIIa inhibitor 31.6 %, any heparin 83.2 %
Roe, 2005 [12] (*USA*) [PMID: 16043682]	Prospective, multi-center, observational registry (NRMI) †	185,968 ACS patients, of which 132,551 NSTEMI, enrolled from 1247 hospitals	**I.** aspirin 84.9 %, BB 72.2 % **II.** ACE 51.2 %, aspirin 83.8 %, BB 78.3 %, statin 85.7 %
Roe, 2006 [35] (*USA*) [PMID: 16765118]	Prospective, multi-center, observational registry (CRUSADE) †	45,744 NST-ACS, enrolled from 424 hospitals	**I.** aspirin 91.2 %, BB 77.8 %, clopidogrel 40.0 %, GP IIb/IIIa inhibitor 35.2 %, any heparin 82.4 %

Abbreviations: ACE, angiotensin-converting-enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensin II AT1 receptor blockers; BB, beta-blocker; CRUSADE, Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines; GP IIb/IIIa, Glycoprotein IIb/IIIa receptor inhibitors; GRACE, Global Registry of Acute Coronary Events; NRMI, National Registry of Myocardial Infarction; NST-ACS, non-ST-elevation acute coronary syndrome; NSTEMI, non-ST-elevation myocardial infarction; PMID, PubMed ID; UA, unstable angina; †Concern large registries that provide access to quality improvement tools, e.g. quarterly feedback reports/benchmarks.

Table 2.2 Characteristics of studies on the extent of adherence to pharmacological therapies recommended by the ACC/AHA and/or ESC NST-ACS guidelines (continued)

First author, year *(country)* [PMID]	**Study design**	Sample	**Main results** *I = acute pharmacological care (<24 h after admission) II = discharge medications*
Roe, 2006 [34] (*USA*) [PMID: 16781220]	Prospective, multi-center, observational registry (CRUSADE) †	77,760 NST-ACS patients, enrolled from 457 hospitals.	**I.** aspirin 91.5 %, BB 78.8 %, GP IIb/IIIa inhibitor 54.2 %, any heparin 83.1 % **II.** ACE/ARB 60.6 %, aspirin 89.7 %, BB 83.4 %, clopidogrel 53.5 %, statin 79.7 %
Roe, 2007 [36] (*USA*) [PMID: 17709638]	Prospective, multi-center, observational registry (CRUSADE) †	55,994 NST-ACS, enrolled from 301 hospitals	**I.** aspirin 91.8 %, BB 78.5 %, clopidogrel 42.5 %, GP IIb/IIIa inhibitor 37.7 %, any heparin 83.4 % **II.** ACE 60.7 %, aspirin 90.8 %, BB 83.9 %, clopidogrel 56.3 %, statin 80.7 %
Schiele, 2005 [48] (*France*) [PMID: 15681575]	Prospective, multi-center, observational registry	754 ACS patients, of which 421 NSTEMI patients, enrolled from 12 hospitals	Median compliance index: 0.66∞ **I.** aspirin 92.0 %, BB 61.0 %, GP IIb/IIIa inhibitors 31.0 %, any heparin 94.0 %
Sherwood, 2014 [40] (*USA*) [24732921]	Prospective, multi-center, observational registry (GWTG-CAD) †	158,492 NSTEMI patients, enrolled from 548 hospitals	**I.** thienopyridine 54.9 % **II.** thienopyridine 73.9 % *(Based on latest measurement in 2012)*
Sinon, 2014 [61] (*Philippines*) [not availiable]	Descriptive multi-center study	1068 NST-ACS patients, enrolled from 39 hospitals	**I.** aspirin 75.28 %, BB 53.84 %, clopidorel 78.0 %, GP IIb/IIIa inhibitor 0.47 %, any heparin 85.67 %
Somma, 2012 [13] (*USA*) [PMID: 22949493]	Prospective, multi-center, observational registry (GWTG-CAD) †	72,352 ACS patients, of which 48,966 NSTEMI, enrolled from 237 hospitals	**I.** aspirin 97.1 %, BB 90.8 % **II.** ACE/ARB 77.4 %, aspirin 97.3 %, BB 97.0 %, clopidogrel 67.0 %, statin 88.0 %
Sonel, 2005 [38] (*USA*) [PMID: 15769762]	Prospective, multi-center, observational registry (CRUSADE) †	43,317 NST-ACS patients, enrolled from 400 hospitals.	**I.** aspirin 91.0 %, BB 77.6 %, clopidogrel 39.5 %, GP IIb/IIIa inhibitor 34.9 %, any heparin 82.5 % **II.** ACE/ARB 60.1 %, aspirin 89.5 %, BB 82.8 %, clopidogrel 52.2 %, statin 74.4 %
Tang, 2005 [63] (*New-Zealand*) [PMID: 16224502]	Retrospective, cross-sectional, single-center, observational study	577 ACS patients, of which 239 NSTEMI and 143 UA, enrolled from 1 hospital	**I.** clopidogrel 59.0 % NSTEMI, GP IIb/IIIa inhibitors 37.0 % NSTEMI, any heparin 93.0 % UA/NSTEMI
Valli, 2014 [52] (*Italy*) [26562982]	Pilot study	121 NSTEMI patients, enrolled from 7 Emergency departments	**I.** aspirin 58.7 %, thienopyridine 48.8 %, any heparin 64.5 %

Abbreviations: ACE, angiotensin-converting-enzyme inhibitor; BB, beta-blocker; CRUSADE, Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines; GP IIb/IIIa, Glycoprotein IIb/IIIa receptor inhibitors; GWTG-CAD, Get With the Guidelines - Coronary Artery Disease; NST-ACS, non-ST-elevation acute coronary syndrome; NSTEMI, non-ST-elevation myocardial infarction; PMID, PubMed ID. †Concern large registries that provide access to quality improvement tools, e.g. quarterly feedback reports/benchmarks.

Table 2.2 Characteristics of studies on the extent of adherence to pharmacological therapies recommended by the ACC/AHA and/or ESC NST-ACS guidelines (continued)

First author, year *(country)* [PMID]	**Study design**	Sample	**Main results** *I = acute pharmacological care (<24 h after admission) II = discharge medications*
Vikman, 2003 [49] (*Finland*) [PMID: 12944205]	Prospective multi-center, observational registry (FINACS I)	501 NST-ACS, enrolled from 9 hospitals	**I.** aspirin 87.0 %, BB 92.0 %, clopidogrel 16.0 %, heparin LMW 76.0 %, GP IIb/IIIa inhibitor 18.0 % **II.** statin 58.0 %
Zeymer, 2014 [51] (*Germany*) [PMID: 25374386]	Prospective, multi-center, observational registry (EPICOR)	333 NST-ACS patients, enrolled from 29 hospitals	**I.** aspirin 96.1 %, BB 94.6 %, thienopyridine 95.5 % (73.0 % clopidogrel / 22.5 % prasugrel), GP IIb/IIIa inhibitors 18.9 %, any heparin 96.7 % **II.** ACE 89.5 %, aspirin 95.2 %, BB 91.3 %, thienopyridine 83.2 % (62.8 % clopidogrel / 20.4 % prasugrel), statin 92.2 %
Zhang, 2009 [59] (*China*) [PMID: 19323898]	Prospective, multi-center observational registry (GRACE) †	618 NST-ACS, enrolled from 12 hospitals.	**I.** aspirin 95.6 %, thienopyridine 85.9 %, GP IIb/IIIa inhibitors 1.8 %, any heparin 90.6 %

Abbreviations: ACE, angiotensin-converting-enzyme inhibitor; BB, beta-blocker; GP IIb/IIIa, Glycoprotein IIb/IIIa receptor inhibitors; GRACE, Global Registry of Acute Coronary Events; LMW, low molecular weight; NST-ACS, non-ST-elevation acute coronary syndrome; NSTEMI, non-ST-elevation myocardial infarction; PMID, PubMed ID. †Concern large registries that provide access to quality improvement tools, e.g. quarterly feedback reports/benchmarks.

Table 2.3 Characteristics of studies on adherence to ACC/AHA and ESC NST-ACS guideline recommendations regarding performing coronary angiography

First author, year *(country)* [PMID]	**Study design**	**Sample**	**Main results** *I = acute pharmacological care (<24 h after admission)* *II = discharge medications*
Bhatt, 2004 [24] *(USA)* [PMID: 15523070]	Prospective, multi-center, observational registry (CRUSADE) †	17,926 NST-ACS patients, enrolled from 248 hospitals	62.2 % CA in-hospital 44.8 % CA <48 h
Chandra, 2009 [25] (*USA*) [PMID: 19282062]	Prospective, multi-center, observational registry (CRUSADE) †	33,238 NST-ACS patients, enrolled from 344 hospitals	83.2 % CA in-hospital 47.5 % CA ≤24 h 65.8 % CA ≤48 h
Diercks, 2006 [26] (*USA*) [PMID: 16824844]	Prospective, multi-center, observational registry (CRUSADE) †	80,845 NST-ACS patients (Number of hospitals unknown)	70.4 % CA in-hospital 49.4 % CA ≤48 h
Diercks, 2007 [27] (*USA*) [PMID: 17496494]	Prospective, multi-center, observational registry (CRUSADE) †	42,780 NST-ACS patients, enrolled from 550 hospitals.	74.5 % CA in-hospital 22.7 % CA ≤24 h 47.8 % CA ≤48 h
Ellis, 2004 [62] (*New Zealand*) [PMID: 15326506]	Prospective, multi-center, observational audit	930 ACS patients, of which 333 UA and 287 NSTEMI, enrolled from 36 hospitals	35.0 % CA in-hospital (NSTEMI patients) 16.0 % CA in-hospital (UA patients)
Ferreira, 2004 [46] (*Portugal*) [PMID: 15641292]	Prospective, multi-center, observational registry (National Registry of ACS)	7,348 ACS patients, of which 2,858 NSTEMI and 1,154 UA, enrolled from 44 hospitals	51.0 % CA in-hospital (NSTEMI patients) 60.0 % CA in-hospital (UA patients)
Kassaian, 2015 [60] (*Iran*) [26671947]	Prospective, multi-center, observational registry	1226 NST-ACS patients, enrolled from 11 hospitals	64.7 % CA in-hospital
Lee, 2008 [55] (*Canada*) [PMID: 18268170]	Prospective, multi-center, observational registry (Canadian ACS II)	2,136 NST-ACS patients, enrolled from 36 hospitals	64.7 % CA in-hospital. Of patients not referred for CA: 59.1 % were found to be at intermediate to high risk according to their TIMI risk score and 70.2 % according to their GRACE risk score. According to their level of risk, 73.7 % of low risk, 73.7 % of intermediate and 54.9 % of high risk patients were referred for CA.
Mandelzweig, 2006 [42] (*32 countries in Europe and Mediterranean basin*) [PMID: 16908490]	Prospective, multi-center, observational survey (EHS-ACS-II)	6,358 ACS patients, of which 3,063 NST-ACS, enrolled from 190 hospitals	62.9 % CA in-hospital
Mehta, 2006 [31] (*USA*) [PMID: 17030838]	Prospective, multi-center, observational registry (CRUSADE) †	113,595 NST-ACS patients, enrolled from 434 hospitals	67.3 % CA in-hospital 34.6 % CA ≤24 h 50.1 % CA ≤48 h

Abbreviations: ACS, acute coronary syndrome; CA, coronary angiography; CRUSADE, Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines; EHS-ACS-II, Second Euro Heart Survey on Acute Coronary Syndrome; NST-ACS, non-ST-elevation acute coronary syndrome; NSTEMI, non-ST-elevation myocardial infarction; PMID, PubMed ID; UA, unstable angina; †Concern large registries that provide access to quality improvement tools, e.g. quarterly feedback reports/benchmarks.

Table 2.3 Characteristics of studies on adherence to ACC/AHA and ESC NST-ACS guideline recommendations regarding performing coronary angiography (continued)

First author, year *(country)* [PMID]	**Study design**	**Sample**	**Main results** *I = acute pharmacological care (<24 h after admission) II = discharge medications*
Nieuwlaat, 2004 [43] (*The Netherlands*) [PMID: 15497784]	Prospective, multi-center, observational survey	421 ACS patients, of which 198 NST-ACS, enrolled from 6 hospitals.	56.0 % CA in high risk patients 25.0 % CA in low risk patients
Peterson, 2008 [33] (*USA*) [PMID: 19032998]	Prospective, multi-center, observational registry (NRMI) †	2,515,106 ACS patients, of which 1,368,497 NSTEMI, enrolled from 2157 hospitals	70.0 % CA in-hospital
Polonski, 2007 [44] (*Poland*) [PMID: 17853315]	Prospective, multi-center observational registry (Polish registry of ACS)	100,193 ACS patients, of which ±42,281 UA and ±26,651 NSTEMI, enrolled from 417 hospitals	31.7 % CA in-hospital (NSTEMI patients) 29.4 % CA in-hospital (UA patients)
Roe, 2005 [37] (*USA*) [PMID: 16157831]	Prospective, multi-center, observational registry (CRUSADE) †	23,298 NST-ACS patients (number of hospitals unknown)	66.1 % CA in-hospital 29.8 % CA ≤24 h 44.9 % CA ≤48 h
Roe, 2006 [35] (*USA*) [PMID: 16765118]	Prospective, multi-center, observational registry (CRUSADE) †	45,744 NST-ACS, enrolled from 424 hospitals	66.3 % CA in-hospital 46.0 % CA ≤48 h
Roe, 2006 [34] (*USA*) [PMID: 16781220]	Prospective, multi-center, observational registry (CRUSADE) †	77,760 NST-ACS patients, enrolled from 457 hospitals.	61.9 % CA in-hospital 42.5 % CA ≤48 h
Roe, 2007 [36] (*USA*) [PMID: 17709638]	Prospective, multi-center, observational registry (CRUSADE) †	55,994 NST-ACS, enrolled from 301 hospitals	72.7 % CA in-hospital 51.5 % CA ≤48 h
Schiele, 2005 [48] (*France*) [PMID: 15681575]	Prospective, multi-center, observational registry	754 ACS patients, of which 421 NSTEMI patients, enrolled from 12 hospitals	64.0 % CA in-hospital
Sonel, 2005 [38] (*USA*) [PMID: 15769762]	Prospective, multi-center, observational registry (CRUSADE) †	43,317 NST-ACS patients, enrolled from 400 hospitals.	66.1 % CA in-hospital, of which 81.5 % of low risk patients and 53.8 % of high risk patients received CA. 47.4 % CA ≤48 h, of which 62.7 % of low risk patients and 33.7 % of high risk patients received CA.
Tang, 2005 [63] (*New-Zealand*) [PMID: 16224502]	Retrospective, cross-sectional, single-center, observational study	577 ACS patients, of which 239 NSTEMI and 143 UA, enrolled from 1 hospital	73.0 % CA in-hospital

Abbreviations: ACS, acute coronary syndrome; CA, coronary angiography; CRUSADE, Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines; NRMI, National Registry of Myocardial Infarction; NST-ACS, non-ST-elevation acute coronary syndrome; NSTEMI, non-ST-elevation myocardial infarction; PMID, PubMed ID; UA, unstable angina; †Concern large registries that provide access to quality improvement tools, e.g. quarterly feedback reports/benchmarks.

Table 2.3 Characteristics of studies on adherence to ACC/AHA and ESC NST-ACS guideline recommendations regarding performing coronary angiography (continued)

First author, year *(country)* [PMID]	**Study design**	**Sample**	**Main results** *I = acute pharmacological care (<24 h after admission) II = discharge medications*
Tricoci, 2006 [39] (*USA*) [PMID: 17056321]	Prospective, multi-center, observational registry (CRUSADE) †	87,640 NST-ACS patients, enrolled from 338 hospitals	61.0 % CA ≤48 h (Based on last measurement, n=29.586 NSTEMI patients)
Vikman, 2003 [49] (*Finland*) [PMID: 12944205]	Prospective multi-center, observational registry (FINACS I)	501 NST-ACS, enrolled from 9 hospitals	41.2 % CA in-hospital
Yan, 2007 [56] (*Canada*) [PMID: 17533203]	Prospective, multi-center, observational registry (Canadian ACS 1 and 2)	4,414 NST-ACS patients, enrolled from 51 (ACS1) and 36 hospitals (ACS2)	63.5 % CA in-hospital, of which 73.8 % of low risk patients, 66.9 % of intermediate patients and 49.7 % of high risk patients received CA. (Based on ACS 2 data, n=1580 NSTEMI patients)
Zeymer, 2014 [51] (*Germany*) [PMID: 25374386]	Prospective, multi-center, observational registry (EPICOR)	333 NST-ACS patients, enrolled from 29 hospitals	95.8 % CA in-hospital

Abbreviations: ACS, acute coronary syndrome; CA, coronary angiography; CRUSADE, Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines; NST-ACS, non-ST-elevation acute coronary syndrome; NSTEMI, non-ST-elevation myocardial infarction; PMID, PubMed ID; UA, unstable angina; †Concern large registries that provide access to quality improvement tools, e.g. quarterly feedback reports/benchmarks.

Table 2.4 Overview of included studies on the association between guideline adherence and adverse cardiac events

First author, year *(country)* [PMID]	Study design	Sample	Guideline recommendations† I	II	III	IV	Univariate associations with occurrence of adverse cardiac events‡ *Significance level: p≤0.05*
Bhatt, 2004 [24] (*USA*) [PMID: 15523070]	Prospective, multi-center, observational registry (CRUSADE)§	17,926 NST-ACS patients, enrolled from 248 hospitals			X		Patients who underwent early CA (<48 h after hospital admission) (vs. not receiving early CA) had significantly: • lower in-hospital mortality (2.0 % versus 6.2 %, AOR 0.63; 95%CI 0.52-0.77); • lower composite endpoint of death/MI (4.7 % versus 8.9 %, AOR 0.79; 95%CI 0.69-0.90)
Dziewierz, 2007 [45] (*Poland*) [PMID: 17496494]	Prospective, multi-center, observational registry (Malopolska registry of ACS)	807 NSTEMI patients, enrolled from 29 hospitals	X				Being prescribed aspirin, clopidogrel, BB, ACE/ARB and statins (vs. not receiving such therapies) was significantly associated with: • a lower risk of in-hospital death, as for every unit of increase on the pharmacotherapy index∞ the risk of death decreased by 46.0 %
Hoekstra, 2005 [28] (*USA*) [PMID: 15863399]	Prospective, multi-center, observational registry (CRUSADE)§	56,804 NST-ACS patients, enrolled from 443 hospitals	X				Being prescribed with early GP IIb/IIIa inhibitors (vs. not receiving early GP IIb/IIIa inhibitors) was significantly associated with: • lower in-hospital mortality (2.7 % versus 4.7 %) • lower composite endpoint of death/MI (5.7 % versus 7.7 %)
Lee, 2008 [55] (*Canada*) [PMID: 18268170]	Prospective, multi-center, observational registry (Canadian ACS II)	2,136 NST-ACS patients, enrolled from 36 hospitals			X		Patients who underwent in-hospital CA (vs. patients not receiving in-hospital CA) had significantly: • lower in-hospital mortality (0.8 % versus 3.7 %) and lower 1-year mortality (4.0 % versus 10.9 %). • higher rates of MI (6.8 % versus 2.4 %) • higher composite endpoint of death/MI (7.1 % versus 5.0 %). However 1 year after discharge patients had lower rates of death/MI (12.5 % versus 16.4 %).
Miller, 2007 [29] (*USA*) [PMID: 17679127]	Prospective, multi-center, observational registry (CRUSADE)§	72,054 NST-ACS patients, enrolled from 509 hospitals	X				Being prescribed acute BB <24 h after admission (vs. not receiving acute BB) was significantly associated with: • lower in-hospital mortality (3.9 % versus 6.9 %, AOR 0.66; 95%CI 0.60-0.72) • lower MI (3.0 % versus 3.6 %, AOR 0.80, 95%CI 0.72-0.89).
Peterson, 2003 [32] (*USA*) [PMID: 12849658]	Prospective, multi-center, observational registry (NRMI)§	60,770 NSTEM patients, enrolled from 1189 hospitals	X				Being prescribed with early GP IIb/IIIa inhibitors <24 h after admission (vs. not receiving early GP IIb/IIIa inhibitors) was significantly associated with: • lower unadjusted mortality (3.3 % versus 9.6 %), lower adjusted mortality (AOR 0.88; CI95% 0.79-0.97) • lower death/MI (4.5 % versus 10.3 %) • higher rates of MI (1.5 % versus 1.1 %)

Table 2.4 Overview of included studies on the association between guideline adherence and adverse cardiac events (continued)

First author, year *(country)* [PMID]	Study design	Sample	Guideline recommendations† I	II	III	IV	Univariate associations with occurrence of adverse cardiac events‡ *Significance level: p≤0.05*
Peterson, 2006 [19] (*USA*) [PMID: 16639050]	Prospective, multi-center, observational registry (CRUSADE)§	64,775 NST-ACS patients, enrolled from 350 hospitals	**X**			**X**	Hospitals with higher guideline adherence rates had significantly: • lower in-hospital mortality rates (4.15 % for highest adherence quartile versus 6.31 % for lowest adherence quartile, AOR 0.81; 95%CI 0.68-0.97) • Every 10 % increase in composite adherence score = 10 % reduction in mortality rate (AOR 0.90; 95%CI 0.84-0.97)

Abbreviations: ACE, angiotensin-converting-enzyme inhibitor; ACS; acute coronary syndromes; ARB, angiotensin II AT1 receptor blockers; BB, beta-blocker; CA, coronary angiography; CRUSADE, Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines; GP IIb/IIIa, Glycoprotein IIb/IIIa receptor inhibitors; MI, myocardial infarction; NST-ACS, Non-ST-Elevation Acute Coronary Syndromes; NSTEMI, non-ST-elevation myocardial infarction; NRMI, National Registry of Myocardial Infarction.

†class I guideline recommendation: I = acute pharmacological care (<24 h after admission), II = risk stratification, III = invasive procedures, IV = discharge medications. ‡Only significant associations are presented, and where possible adjusted odds ratios (AOR) and their 95% confidence intervals (CI) are provided. §Concern large registries that provide access to quality improvement tools, e.g. quarterly feedback reports/benchmarks. ∞Pharmacotherapy index: range from 0-7, one point for each medication received, ASA, clopidogrel, GB IIa/IIIb inhibitor, LMW Heparin, BB, ACE/ARB and statin.

Association between guideline adherence and adverse cardiac events

Seven of the included studies reported on the association between guideline adherence and occurrence of adverse cardiac events (i.e., death and/or MI) in NST-ACS patients [19,24,28,29,32,45,55] (Table 2.4). Overall, in all studies, higher adherence to guideline recommendations was significantly associated with a lower occurrence of death or the composite endpoint of death/MI. For example, patients who received early treatment with glycoprotein IIb/IIIa inhibitors [28] or underwent in-hospital CA [24] had lower mortality rates than patients who did not receive such therapies. Mixed results were found for the association between guideline adherence and the occurrence of myocardial infarction (MI). In one study higher guideline adherence was associated with lower rates of MI [29], whereas in two studies higher guideline adherence was associated with higher rates of MI [32,55]. In two other studies, no significant association between guideline adherence and MI was found [24,28].

Potential factors associated with guideline adherence

Fifteen of the included studies examined potential factors that were associated with lower or higher guideline adherence [19,24,25,28-30,32,34,37,49,50,53,56,57,64] (Figure 2.2, Table 2.5). Of these, eight studies reported on factors associated with adherence to guideline recommendations on acute in-hospital pharmacological treatment [19,25,28,29,32,34,53,56]. In addition, four studies reported on potential factors influencing adherence to the performance of in-hospital CA [24,37,49,56], whereas seven studies reported on potential factors related to the prescription of discharge medications [19,28-30,34,57,64]. One study reported on potential factors associated with adherence to recommendations on risk stratification [50]. Overall, these factors could be categorized in either patient-related or organization-related factors.

Acute in-hospital pharmacological treatment

The following *patient-related* factors were associated with *higher* prescription rates of acute in-hospital pharmacological treatment: white race [28,32], hypercholesterolemia[28,29], (recent) smoker [28,32], hypertension [28], family history of coronary artery disease [28,29], prior beta-blocker use [29], high admission blood pressure [29], positive cardiac markers (e.g. troponin, CK-MB, CK) [28,34], transient ST-elevation or ST-depression on the ECG [28,29,34], and receiving CA in-hospital or within 24 h after admission [53]. On the contrary, the following patient-related factors were related to *lower* prescription of acute in-hospital pharmacological treatment: older age [28,29,32,34], female gender [28,29,32], high admission heart rate [28,29], chronic heart failure [28,29,53], prior stroke [28], prior MI [28], prior CABG [28], diabetes mellitus [34], acute in-hospital heart failure [28,29,34], kidney failure [28,29,34], bleeding [53], high GRACE risk status [53,56], and presentation at the hospital with cardiac arrest [53]. Mixed results were found for factors prior percutaneous coronary

intervention (PCI) and health-insurance, which were in some studies associated with higher prescription rates of acute in-hospital pharmacological treatment [29,32,53], whereas in other studies they were related to lower prescription rates [28,29]. On an *organizational* level, patients with a cardiologist as their primary care provider [19,28,29,34], patients treated at hospitals accredited by the Society of Cardiovascular Patient Accreditation (SCPC) [25], and patients treated at hospitals with a teaching status [29] or cardiac surgery facilities (e.g., facilities for coronary artery bypass grafting (CABG) surgery) [19] were *more likely* to receive acute in-hospital pharmacological treatment. Patients treated at hospitals with catheterization, but no cardiac surgery, facilities were less likely to receive such treatment [53].

Performing in-hospital CA

Patient-related factors, including white race [24], high admission blood pressure [24], hypercholesterolemia [24], (recent) smoking [24], high body mass index [24], positive family history for CAD [24], prior PCI [24], positive cardiac markers (e.g. troponin, CK-MB, CK) [24,37,49], and transient ST- elevation or ST-depression on the ECG [24,49], were associated with *higher* performance rates of in-hospital CA. On the other hand, older age [24,49], female gender [24,56], high admission heart rate [24], chronic heart failure [24], diabetes mellitus [24,49], in-hospital heart failure [24], prior stroke [24], kidney failure [24], high GRACE risk status [56], prior CABG [24], prior MI [24], presenting in-hospital during off-hours [24], and having no insurance or a Medicare insurance [24] were related to *lower* performance rates of in-hospital CA. On an *organizational* level, factors such as, patients treated at hospitals with catheterization [56], PCI [24], or cardiac surgery facilities [24], patients from the Midwest/west region (USA) (geographical location) [24] and patients with a cardiologist as their primary care provider [24,56] were *more likely* to receive in-hospital CA. However, patients admitted at larger size hospitals (i.e., higher number of hospital beds) [24], and patients from Northeast region (USA) (geographical location) [24] were *less likely* to receive in-hospital CA. Mixed results were found on an organizational level with regard to a hospital's teaching status, with in one study this factor being associated with *higher* performance rates of in-hospital CA [49], whereas in another study this factor was associated with *lower* CA-rates [24].

Risk stratification

The following *patient-related* factors were associated with *higher* cardiac risk score use: obesity and former smoker, whereas a diagnosis of unstable angina (versus NSTEMI), being resuscitated in-hospital, acute heart failure and tachycardia were associated with *lower* cardiac risk score use [50].

Discharge medications

The following *patient-related* factors were associated with *higher* prescription rates of discharge medications: white race [30], high admission blood pressure [30], hypercholesterolemia [30], (recent) smoking [30], angina pectoris [64], peripheral artery disease [30], prior PCI [30], prior CABG [30], prior MI [30,64], diabetes mellitus [30], hypertension [64], prior clopidogrel use [30,57], risk factors for coronary artery disease [57], positive cardiac markers (e.g. troponin, CK-MB, CK) [30,34], transient ST-elevation or ST-depression on the ECG [34], and receiving in-hospital CA [30]. On the contrary, older age [34,64], female gender [64], high admission heart rate [30], chronic heart failure [64], high GRACE risk status [56], diagnosis of NSTEMI [57], prior heparin use [30], kidney failure [34], ejection fraction of less than 40% [30], bleeding [30], atrial fibrillation [64], and in-hospital cardiogenic shock [64] were associated with *lower* prescription of discharge medications. Mixed results were found for in-hospital heart failure, prior stroke, and low hemoglobin levels, with in some studies these factors being associated with *higher* prescription rates of discharge medications [57], whereas in other studies opposite associations were found [30, 64]. On an *organizational* level, NST-ACS patients treated at hospitals with cardiac surgery facilities [19], as well as patients with a cardiologist as their primary care provider [19,34] were more likely to receive recommended discharge medications, whereas patients admitted to hospitals with lower quality measures on MI-care [30] were less likely to receive guideline recommended pharmacological discharge care. Regarding the factor geographical location, the extent of adherence depended on the type of country where treatment was provided [64].

All guideline recommendations

The following *patient-related* factors were associated with *higher* adherence to three or more guideline recommendations: white race, high blood pressure, hypercholesterolemia, (recent) smoker, positive cardiac markers (e.g. troponin, CK-MB, CK), transient ST elevation or ST depression on the electrocardiogram. On the contrary, elder age, female gender, high heart rate, chronic or acute heart failure, kidney failure, high GRACE risk status, were related to *lower* guideline adherence. On an *organizational* level, the presence of cardiac surgery facilities (e.g. CABG) and having a cardiologist as the primary care provider were associated with *higher* guideline adherence.

Table 2.5 Potential factors associated with guideline adherence

Type of factor	Factor	Main results†	Guideline recommendations‡∞ I	II	III	IV
Patient	**Demographics**					
	Age	Elderly patients were less likely to receive acute aspirin, BB, heparin [34] and GP IIb/IIIa inhibitors [28,32], CA ≤48 h or in-hospital [24,49], statin [34], and all guideline recommended therapies (i.e. ACE, aspirin, BB, statin) [64] at discharge than younger patients	↓		↓	↓
		Patients' aged between 55 years and 74 years were less likely to receive acute BB [29] than patients below 55 years or of 75 years and older	↓			
	Gender	Female patients were less likely to receive acute BB [29] and GP IIb/IIIa inhibitors [28,32], to receive CA ≤48 h or in-hospital [24,56], and to receive all guideline recommended discharge therapies (i.e. ACE, aspirin, BB, statin) [64] than male patients	↓		↓	↓
	Race	Patients of white race were more likely to receive acute GP IIb/IIIa inhibitors [28,32], CA ≤48 h [24], and clopidogrel at discharge [30] than patients of a non-white race	↑		↑	↑
	Clinical factors					
	Angina pectoris	Patients with a history of angina pectoris were more likely to receive all guideline recommended discharge therapies (i.e. ACE, aspirin, BB, statin), than patients without a history of angina pectoris [64]				↑
	CHF	Patients with chronic heart failure were less likely to receive acute antiplatelet therapy (e.g. clopidogrel) [53], BB [29] and GP IIb/IIIa inhibitors [28], to receive CA ≤48 h [24], and all guideline recommended discharge therapies (i.e. ACE, aspirin, BB, statin) [64], than patients without chronic heart failure	↓		↓	↓
	PAD	Patients with PAD were more likely to be prescribed with clopidogrel at discharge, than patients without PAD [30]				↑
	Prior PCI	Patients with a prior PCI were more likely to receive acute antiplatelet therapy (e.g. clopidogrel) [53] and GP IIb/IIIa inhibitors [32], to receive CA ≤48 h [24], and to receive clopidogrel at discharge [30], than patients without a PCI in their medical history	↑		↑	↑
		Patients with a prior PCI were less likely to be treated with acute BB, than patients without a PCI in their medical history [29]	↓			
	Prior CABG	Patients with a prior CABG were less likely to receive acute GP IIb/IIIa inhibitors [28], and to receive CA ≤48 h [24], than patients without a CABG in their medical history	↓		↓	
		Patients with a prior CABG were more likely to be prescribed with clopidogrel at discharge, than patients without a CABG in their medical history [30]				↑
	Prior MI	Patients with a prior MI were more likely to receive clopidogrel [30] and all guideline recommended therapies (i.e. ACE, aspirin, BB, statin) [64] at discharge, than patients without a MI in their medical history				↑
		Patients who had a prior MI were less likely to receive acute GP IIb/IIIa inhibitors [28], and CA ≤48 h, than patients without a MI in their medical history [24]	↓	↓		
	Prior clopidogrel use	Patients who used clopidogrel before hospitalization were more likely to receive clopidogrel at discharge, than patients who did not use clopidogrel before hospitalization [30, 57]				↑

Table 2.5 Potential factors associated with guideline adherence (continued)

Type of factor	Factor	Main results†	Guideline recommendations‡∞ I	II	III	IV
Patient	**Clinical factors**					
	Prior BB use	Patients who used BB before hospitalization were more likely to receive acute BB, than patients who did not use BB before hospitalization [29]	↑			
	Prior heparin use	Patients who used heparin before hospitalization were less likely to be prescribed with clopidogrel at discharge, than patients who did not use heparin before hospitalization [30]				↓
	Prior stroke	Patients with a prior stroke were less likely to receive acute GP IIb/IIIa inhibitors [28], to receive CA ≤48 h [24], and all guideline recommended therapies (i.e. ACE, aspirin, BB, statin) [64] at discharge, than patients without a stroke in their medical history	↓		↓	↓
		Patients with a prior stroke were more likely to receive clopidogrel at discharge [57], than patients without a stroke in their medical history				↓
	BMI	Patients with a high BMI were more likely to receive CA ≤48 h [24], and more likely to have a risk score documented in their medical chart [50], than patients with a normal BMI		↑	↑	
	CAD risk factors	Patients with two or more risk factors for CAD were more likely to receive clopidogrel at discharge, than patients with one or no risk factors for CAD [57]				↑
	Diabetes mellitus	Patients with diabetes mellitus were less likely to receive acute aspirin [34], and to receive CA ≤48 h or in-hospital [24,49], than patients without diabetes mellitus	↓		↓	
		Patients with diabetes mellitus were more likely to receive clopidogrel [30] and all guideline recommended therapies (i.e. ACE, aspirin, BB, statin) [64] at discharge, than patients without diabetes mellitus				↑
	EF <40%	Patients with an EF <40% were less likely to be prescribed with clopidogrel at discharge, than patients without an EF <40% [30]				↓
	Family history of CAD	Patients with a positive family history for CAD were more likely to receive acute BB [29] and GP IIb/IIIa inhibitors [28], and CA ≤48 h [24] than patients with a negative family history of CAD	↑		↑	
	Heart failure (acute)	Patients with acute heart failure were less likely to receive acute aspirin, heparin [34], GP IIb/IIIa inhibitors [28] and BB [29,34], to receive CA ≤48 h [24], and less likely to receive all guideline recommended discharge therapies (i.e. ACE, aspirin, BB, statin)[64], than patients without acute heart failure. They were also less likely to have a risk score documented in their medical chart [50]	↓	↓	↓	↓
		Patients with acute heart failure were more likely to be prescribed with ACE at discharge, than patients without acute heart failure [34]				↑
	Hypercholesterolemia	Patients with hypercholesterolemia were more likely to receive acute BB [29] and GP IIb/IIIa inhibitors [28], to receive CA ≤48 h [24], and to receive clopidogrel at discharge [30], than patients without hypercholesterolemia	↑		↑	↑

Table 2.5 Potential factors associated with guideline adherence (continued)

Type of factor	Factor	Main results†	Guideline recommendations‡∞ I	II	III	IV
Patient	**Clinical factors**					
	Hypertension	Patients with a history of hypertension were more likely to receive acute GP IIb/IIIa inhibitors [28], and to receive all guideline recommended discharge therapies (i.e. ACE, aspirin, BB, statin) [64], than patients without a history of hypertension	↑			↑
	Kidney failure	Patients with kidney failure were less likely to receive acute aspirin, heparin [34], BB [29] and GP IIb/IIIa inhibitors [28], to receive CA ≤48 h [24], and to receive aspirin and ACE at discharge [34], than patients without kidney failure	↓		↓	↓
	NSTEMI	NSTEMI patients were less likely to receive clopidogrel at discharge than patients with UA [57], but were more likely to have a risk score documented in their medical chart [50]		↑		↓
	Risk status (GRACE)	Patients with a high risk status are less likely to receive acute antiplatelet therapy [53] and other acute medications [56], to receive CA, and appropriate discharge medications [56] compared to patients with a low risk status	↓		↓	↓
	Smoking	(Recent) smokers were more likely to receive acute GP IIb/IIIa inhibitors [28,32], CA ≤48 h [24], and clopidogrel at discharge [30], than non-smokers (Recent) smokers were also more likely to have a risk score documented in their medical chart than non-smokers [50]	↑	↑	↑	↑
	Bleeding	Patients with a major bleeding in their medical history were less likely to be treated with antiplatelet therapy (e.g. clopidogrel) [53] or to receive clopidogrel at discharge [30], than patients without a major bleeding	↓			↓
	Hemodynamics					
	Blood pressure	Patients with a high blood pressure at admission were more likely to receive acute BB [29], CA ≤48 h [24], and clopidogrel at discharge [30] than patients with a normal blood pressure at admission	↑		↑	↑
	Heart rate	Patients with a high heart rate were less likely to receive acute BB [29] and GP IIb/IIIa inhibitors [28], to receive CA ≤48 h [24], and to receive clopidogrel at discharge [30] than patients with a normal heart rate at admission. They were also less likely to have a risk score documented in their medical chart [50]	↓	↓	↓	↓
	Cardiac arrest / resuscitation	Patients presenting with cardiac arrest or who were resuscitated at hospital-admission were less likely to be treated with acute antiplatelet therapy (e.g. clopidogrel) [53], and less likely to have a risk score documented in their medical chart [50], than patients not presenting with cardiac arrest or being resuscitated in hospital	↓	↓		
	Cardiogenic shock	Patients presenting with cardiogenic shock were less likely to receive all guideline recommended discharge therapies (i.e. ACE, aspirin, BB, statin), than patients without cardiogenic shock [64]				↓
	Laboratory results					
	Cardiac markers (e.g. troponin, CK-MB, CK)	Patients with positive cardiac markers were more likely to receive acute aspirin, BB, heparin [34] and GP IIb/IIIa inhibitors [28], to receive CA ≤48 h or in-hospital [24,37,49], and ACE, aspirin, BB, Statin [34], clopidogrel at discharge [30] than patients with normal cardiac markers levels	↑		↑	↑

Table 2.5 Potential factors associated with guideline adherence (continued)

Type of factor	Factor	Main results†	Guideline recommendations‡∞ I	II	III	IV
Patient	**Laboratory results**					
	HB	Patients with HB levels of 9g/dL or lower were either less likely to receive clopidogrel at discharge [30] or more likely to receive clopidogrel at discharge [57] than patients with normal HB levels				↑ ↓
	Electrocardiogram findings					
	Transient ST elevation	Patients with transient ST elevation were more likely to receive acute aspirin [34], BB [29,34] and heparin [34], to receive CA ≤48 h [24], and to be discharged with aspirin, BB and ACE [34] than patients without such deviations on the electrocardiogram	↑		↑	↑
	ST depression	Patients with ST depression were more likely to receive acute aspirin [34], BB [29,34], heparin [34] and GP IIb/IIIa inhibitors [28], and to receive CA ≤48 h or in-hospital [24, 49] and to be discharged with ACE, aspirin, and BB [34] than patients without such deviations on the electrocardiogram	↑		↑	↑
	Atrial fibrillation	Patients with atrial fibrillation were less likely to receive all guideline recommended discharge therapies (i.e. ACE, aspirin, BB, statin), than patients without such deviation on the electrocardiogram [64]				↓
	Invasive diagnostic procedures					
	CA ≤24 h	Patients catheterized within the first 24 h after admission were more likely to be treated with antiplatelet therapy (e.g. clopidogrel), than patients that were not catheterized within the first 24 h after admission [53]	↑			
	In-hospital CA	Patients receiving CA in-hospital were more likely to receive antiplatelet therapy (e.g. clopidogrel) [53], and to receive clopidogrel at discharge [30] than patients not receiving CA in-hospital	↑			↑
	Other					
	Insurance	Patients with medicare or no insurance were less likely to receive acute BB [29] and GP IIb/IIIa inhibitors [28,32], and to receive CA ≤48 h than patients with private insurance [24] Patients with self-insurance were more likely to receive acute BB [29], but less likely to receive acute GP IIb/IIIa inhibitors [28], than patients with private insurance	↓ ↑		↓	
	Time of presentation	Patients presenting at hospital during off-hours (i.e. between 5 pm to 7 am or in weekends) were less likely to receive CA ≤48 h, than patients presenting between during the week hours between 7 am to 5 pm [24]			↓	
Organization	PCI facilities	Patients treated at hospitals with PCI facilities were more likely to receive CA ≤48 h, than patients treated in hospitals without such facilities [24]			↑	
	CABG facilities	Patients treated at hospitals with surgical facilities were more likely to receive CA ≤48 h [24], and be among centers with the highest adherence rates regarding acute and discharge therapies [19] than patients treated at hospitals without surgical facilities	↑		↑	↑

Table 2.5 Potential factors associated with guideline adherence (continued)

Type of factor	Factor	Main results†	Guideline recommendations‡∞ I	II	III	IV
Organization	**Other**					
	Catheterization facilities	Patients admitted to hospitals with onsite catheterization facilities were less likely to be treated with antiplatelet therapy (e.g. clopidogrel), than patients admitted to hospitals without such facilities [53]	↓			
		Patients admitted to hospitals with onsite catheterization facilities were more likely to receive CA, than patients treated in hospitals without such facilities [56]			↑	
	Cardiology care	Patients cared for by cardiologists were more likely to receive acute aspirin [34], BB [29,34], heparin [34] and GP IIb/IIIa inhibitors [28], to receive CA ≤48 h or in-hospital [24,56], and ACE, aspirin, BB, statin at discharge [34], and to be among centers with the highest adherence rates regarding acute and discharge therapies [19], than patients treated by other specialists	↑		↑	↑
	Geographical location	Patients from the Northeast region (USA) were less likely to receive CA ≤48 h than patients in the south region [24]			↓	
		Patients from the Midwest/west region (USA) were more likely to receive CA ≤48 h than patients in the south region [24]			↑	
		Patients treated in Europe, Australia, New-Zealand and Canada were more likely to receive all guideline recommended discharge therapies (i.e. ACE, aspirin, BB, statin) than patients treated in North America [64]				↑
		Patients treated in Argentina and Brazil were less likely to receive all guideline recommended discharge therapies (i.e. ACE, aspirin, BB, statin) than patients treated in the North America [64]				↓
	Nr. of beds	Patients treated in hospitals with higher numbers of hospital beds were less likely to receive CA ≤48 h, than patients treated in hospital with lower number of hospital beds [24]			↓	
	Accreditation	Patients treated at SCPC accredited hospitals were more likely to receive acute aspirin and BB, than patients not treated in such hospitals [25]	↑			
	Hospitals' teaching status	Patients treated at teaching hospitals were more likely to receive acute BB [29] and to receive CA in-hospital [49], than patients treated in non-teaching hospitals	↑		↑	
		Patients treated at teaching hospitals were less likely to receive CA ≤48 h, than patients treated in non-teaching hospitals [24]			↓	
	Quality of MI care	Patients treated at hospitals with lower quality measures of MI care were less likely to receive clopidogrel at discharge, than patients treated at hospitals with higher quality of care measures of MI care [30]				↓

Abbreviations: ACE, angiotensin-converting-enzyme inhibitor; BB, beta-blocker; BMI, body mass index; CA, coronary angiography; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CHF, chronic heart failure; EF, ejection fraction; GP IIb/IIIa, Glycoprotein IIb/IIIa receptor inhibitors; GRACE, global registry of acute coronary events; HB, hemoglobin; MI, myocardial infraction; NSTEMI, non-ST-elevation myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; SCPC accreditation, society of cardiovascular patient care accreditation; UA, unstable angina. †Factors significantly ($p \leq 0.05$) associated with guideline adherence in multivariable analysis. ‡class I guideline recommendation: I = acute pharmacological care (<24 h after admission), II = risk stratification, III = invasive procedures, IV = discharge pharmacological care. ↑= higher adherence, ↓ = lower adherence. ∞ All factors are derived from studies studying adherence to the ACC/AHA guidelines, except Vikman 2003 (49) & Engel 2015 (50) who studied adherence to the ESC guidelines.

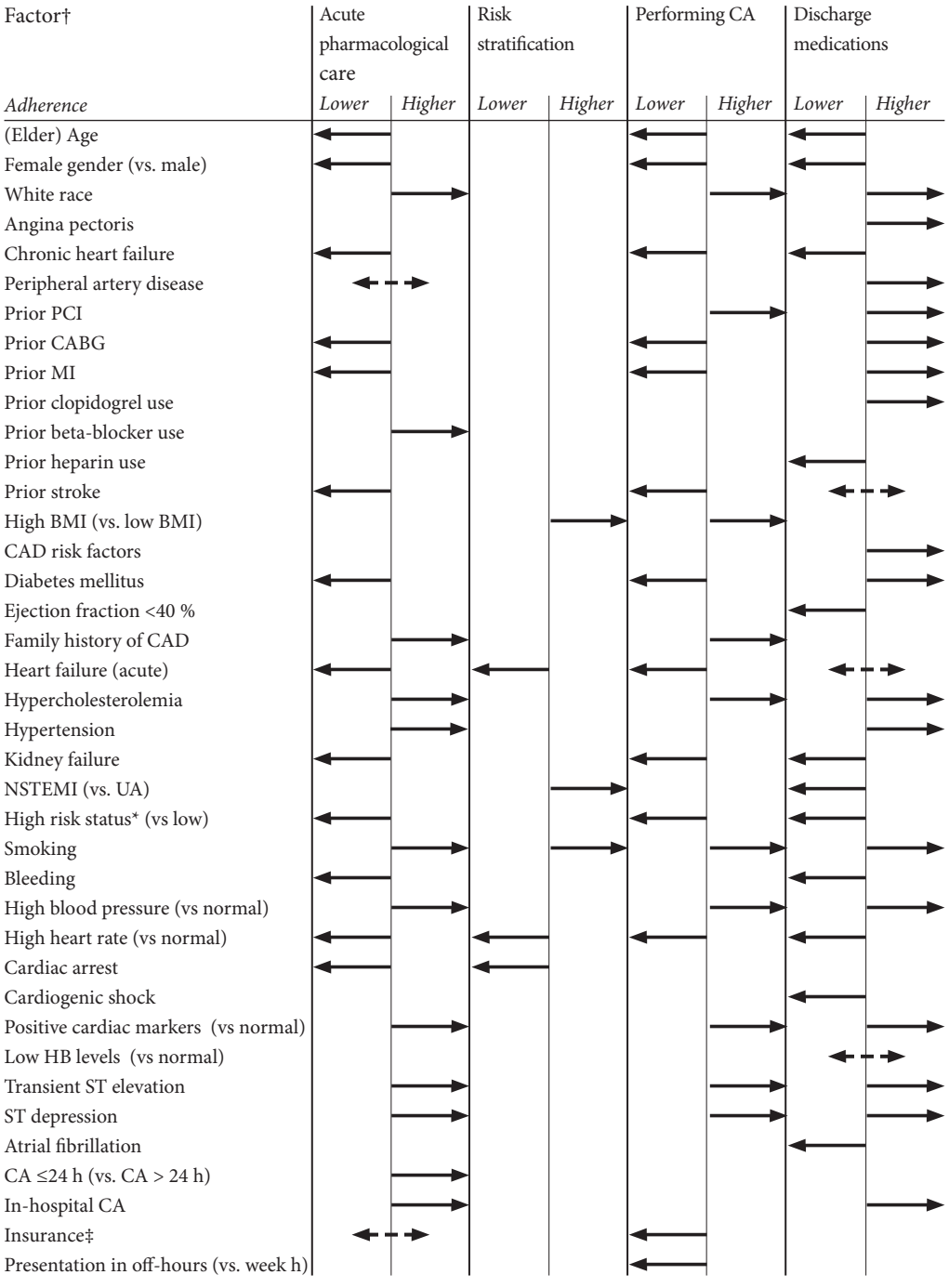
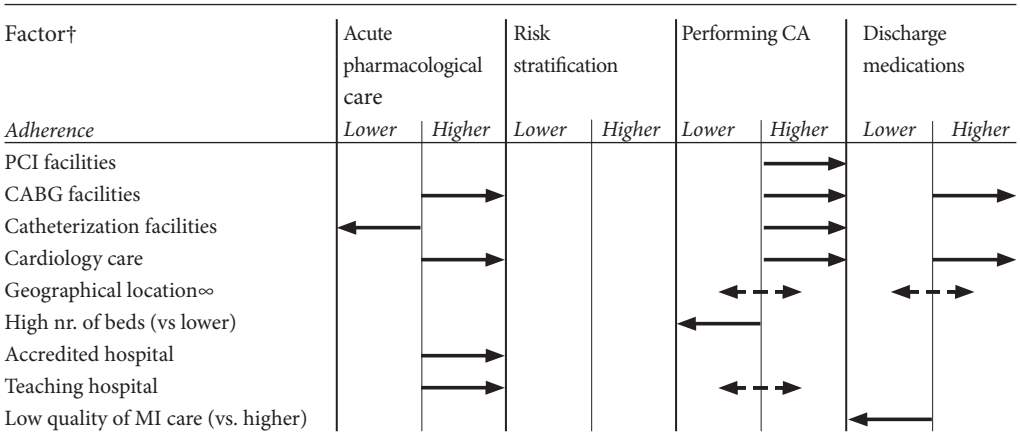


Figure 2.2 Factors significantly ($p \leq 0.05$) associated with lower or higher guideline adherence



† Reference category is the absence of the clinical factor, unless stated otherwise. * Calculated with the GRACE (global registry of acute coronary events) risk score. ‡ Reference category is private insurance, versus self-insurance, medicare insurance or no-insurance. ∞ Reference category is south region, versus northeast and Midwest/west region (USA); and North America versus Europe, Australia, New Zealand, Canada, Argentina and Brazil. Abbreviations: BMI, body mass index; CA, coronary angiography; CABG, coronary artery bypass grafting; CAD, coronary artery disease; HB, haemoglobin, MI, myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; UA, unstable angina.

Figure 2.2 Factors significantly ($p \leq 0.05$) associated with lower or higher guideline adherence (continued)

2.4 Discussion

This systematic literature review examined the extent of adherence to ACC/AHA and ESC guideline recommendations on acute in-hospital pharmacological treatment, risk stratification, performing in-hospital CA, and the prescription of discharge medications in the management of NST-ACS patients. In addition, associations between guideline adherence and adverse cardiac events were examined and potential factors associated with lower or higher guideline adherence were identified.

Results of this systematic literature review showed a wide variation in guideline adherence rates to various cardiac recommendations, possibly reflecting a guideline-practice gap in the management of NST-ACS patients. Adherence rates for pharmacological therapies at admission or at discharge ranged from less than 5.0 % to more than 95.0 %, whereas adherence rates for the performance of in-hospital CA ranged between 16.0 % and 95.8 %, and between 34.3 % and 93.0 % for risk stratification. In addition, although the number of studies reporting on the association between adherence and adverse cardiac events was relatively small, lower guideline adherence was consistently found to be associated with

poorer prognosis (i.e. higher rates of death, and the composite endpoint of death/MI). Finally, several patient-related (e.g. age, gender, presence of co-morbidities) and organization-related factors (e.g. teaching hospital, availability of PCI/CABG facilities) possibly influencing the extent of adherence to different guideline recommendations were identified.

The results of the current systematic literature review corroborate the findings of a previous literature review, in which suboptimal guideline adherence in the management of NST-ACS was demonstrated, with overall 25.0 % of patients not receiving appropriate pharmacological treatment [15]. Our findings also confirm results of studies on guideline adherence in other cardiac patient groups. For example, the wide variation in adherence rates found in this systematic review is in line with previous studies in STEMI patients. In some of these studies rates of 0.0 % to 2.0 % were indicated for adherence to guideline recommendations on pharmacological treatment [65,66], whereas in other studies rates of 98.5 % or even higher were reported [13]. In addition, this wide variation in adherence rates has been demonstrated before in a systematic review comparing guideline adherence between patients with different diseases, including cardiovascular disease, in the pre-hospital and emergency care setting [67]. Overall, adherence to various medical guidelines ranged from 0.0 % to 98.0 % in this study, with the lowest rates found for adherence to recommendations of cardiac guidelines.

Previous studies mentioned several potential reasons for this practice variation, which should be taken into account in the interpretation of our results. First, the majority of included studies concerned registries in which information on guideline adherence was derived from patients' medical records. This way, specific contra-indications providing a legit reason to deviate from the guidelines might be overlooked, as it is known that contra-indications are not always properly documented by attending physicians [68]. Consequently, guideline adherence rates reflected in these studies might be an underestimation of actual adherence rates in clinical practice. Second, it was suggested that physicians sometimes deviate from the guidelines because of inconclusive or insufficient evidence underlying guideline recommendations [16,69]. In this review, low adherence rates were found for the early prescription of glycoprotein IIa/IIIb inhibitors and the early and discharge prescription of clopidogrel. However, at the time of publication of the majority of these studies these pharmacological therapies were relatively new, and therefore probably not yet routinely prescribed. Third, it has been shown that physicians sometimes deviate from the guidelines because of calculated complication risks. For example, cardiologists could argue that it would be better not to perform CA in high-risk patients, because of the risk of bleeding associated with this treatment. However, this kind of decision-making is in contrast with the guidelines, which state that especially high-risk patients should receive guideline-recommended therapies [10,11].

Although over the past years there has been growing evidence regarding the effectiveness of risk stratification methods to guide clinical decision-making for the appropriate treatment, in this literature review only a minority of studies reported on this topic. Of these, three studies reported on the use of ECG findings for risk stratification and two studies reported on the use of troponin assessment. These latter studies were however of poor and moderate methodological quality, so results should be interpreted with caution. In addition, only one of the included studies reported on the use of validated risk-scoring instruments (i.e., GRACE and TIMI risk scores). The lack of studies on this topic could be explained by the fact that the use of these validated risk-scoring instruments in clinical decision making is a relatively new concept, which is mainly highlighted in the latest versions of the ACC/AHA and ESC guidelines. To further examine the actual use of validated risk scoring instruments and other risk stratification methods in clinical practice, and their effects on the quality of care, further research is needed.

Consistent with previous studies in MI and heart failure patients [70-73], in this systematic literature review lower guideline adherence was associated with adverse cardiac outcomes, including higher rates of mortality and death/MI. However, the association between adherence and the composite endpoint of death/MI should be interpreted with caution, as it has been reported before that the magnitude of the effect can differ across different components of a composite endpoint [74-77]. In other words, given that mixed results were found with regard to the association between guideline adherence and MI, the association between lower guideline adherence and higher rates of death/MI seems to be mainly driven by an impact of adherence on mortality rather than infarction. Furthermore, although all the included studies on the relationship between adherence and clinical outcomes had a prospective design, the causality of this relationship needs further investigation. One could argue that it could also be the case that severe progressing symptoms - a poorer prognosis - motivates healthcare professionals to deviate from the guidelines and apply career-based, rather than evidence-based procedures.

In this systematic review a distinction could be made between factors associated with specific guideline recommendations and factors associated with recommendations on all guideline recommendations. In previous studies, in addition to patient- and organization-related factors which were found in this systematic review, also health care provider-related factors were identified as potential associates of guideline adherence. For example, cardiologists' awareness, familiarity, and personal agreement with guidelines and its recommendations have been linked to the extent of adherence to clinical practice guidelines, as well as high workload and accessibility of the guideline [16]. Furthermore, in a study on potential reasons for non-adherence in patients with ischemic heart disease, it was indicated that the inability of guidelines to directly manage the care of individual patients could be a reason

for cardiologists to deviate from guideline recommendations [78]. Given that in our review results on the association between patient- and organization-related factors and guideline adherence were mixed and information on health care provider-related factors was lacking, future research focusing on the influence of patient-, organization-, as well as provider-related factors on guideline adherence in NST-ACS patients is warranted.

Given the large variation in adherence rates and lower guideline adherence being associated with adverse clinical outcomes in several studies, close monitoring of the extent of adherence to the latest ACC/AHA and ESC guidelines for NST-ACS is essential to maintain a high standard of care in this patient group [10,11]. Previously, several quality improvement programs have been developed, aimed to fasten implementation of cardiac guidelines in clinical practice and increase adherence rates [71,79,80]. However, these programs often targeted the entire population of either ACS or NST-ACS patients, rather than focusing on NST-ACS patients in which treatment according to the guidelines have proven to be less likely. Two previous studies in ACS patients evaluated quality improvement initiatives in which implementation strategies were tailored to individual patient characteristics. These studies showed substantial improvements in adherence rates [81,82]. Hence, knowledge on potential patient-, organization-, and provider-related factors influencing guideline adherence in NST-ACS could contribute to the identification of high-risk patients and the development of tailored implementation strategies aimed to increase adherence in this specific patient group [17,83]. Additionally, previous quality improvement programs often focused on implementation of the guideline as a whole, rather than the improvement of adherence to specific guideline recommendations. It is suggested, however, that the latter more tailored approach is possibly more successful in improving adherence, as the current review and also previous studies show that adherence varies largely across individual recommendations [84].

2.4.1 Study limitations

In interpreting the results of this systematic literature review, several limitations should be taken into account. First, due to heterogeneity in study design (e.g., observational versus quasi-experimental, study sample (i.e., NST-ACS, NSTEMI, and/or UA patients), and type of guideline recommendations under study, a meta-analysis was not feasible. Generalizability of study results might therefore be hampered. In addition, study quality scores of the included studies ranged from poor to excellent, which could have distorted the interpretation of study results. However, the impact of these differences is expected to be limited, as the wide variation in adherence rates was prevalent in all different types of studies, including both poor and excellent quality studies.

A second limitation of the current literature review was that the majority of included studies derived their data from patients' medical charts, which may incorporate a high risk of bias.

A third limitation is that only a few of the included studies reported on the latest versions of the ACC/AHA and ESC guidelines, published respectively in 2014 [11] and 2015 [10]. However, guideline recommendations described in the most recent versions of the guidelines are comparable to recommendations in the earlier versions of the ESC and ACC/AHA guidelines included in this review, except for the prescription of glycoprotein IIb/IIIa inhibitors, which degraded from a class 1 recommendation to a class II recommendation in both guidelines. It is recommended that future studies take the newest guidelines into account when studying the extent of adherence in the management of NST-ACS patients, and for instance explore any trends in guideline adherence.

The final limitation concerns the assessment of the methodological quality of the eligible studies by using a checklist based on the STROBE criteria. The STROBE is developed to assist authors in reporting their researcher, rather than assessing study quality. As a consequence bias can be introduced, with the methodological quality reported in this review being an overestimation or underestimation of the actual study quality. However, reliable and generally accepted tools to assess the quality of observational studies are lacking [85].

2.5 Conclusion

Despite NST-ACS being one of the most common types of ACS demanding urgent and guideline-recommended care, results of this systematic literature review indicated that there seems to exist a practice gap in the management of NST-ACS, with a substantial proportion of patients not receiving guideline-recommended care. Consequently, lower adherence might be associated with a higher risk for poor prognosis. Future research should further investigate the complex nature of guideline adherence in this patient group, its impact on clinical care, and potential patient-, organization-, and provider-related factors influencing adherence. This knowledge is essential to optimize clinical management of NST-ACS patients and could guide future quality improvement initiatives.

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A. Systematic review search strategies

A.1 Pubmed (including MEDLINE)

Search	Query	Nr. of hits
#1	Search ("Angina, Unstable"[Mesh] OR (Angina[tw] AND (unstable[tw])	17,138
#2	Search ("Myocardial Infarction"[Mesh] OR (Myocardial infarct*[tw] OR Myocardium infarct*[tw] OR heart infarct*[tw] OR cardiac infarct*[tw]))	212,441
#3	Search ("Acute Coronary Syndrome"[Mesh] OR acute coronary syndrome*[tw])	24,181
#4	Search (#1 OR #2 OR #3)	231,402
#5	Search ("Guideline Adherence"[Mesh] OR (("Guidelines as Topic"[Mesh] OR guideline*[tw] OR protocol*[tw]) AND (adheren*[tw] OR complian*[tw])))	49,064
#6	Search (#4 AND #5)	1303

A.2 EMBASE

Search	Query	Nr. of hits
#1	Search 'unstable angina pectoris'/exp OR (angina:de,ab,ti AND (unstable:de,ab,ti OR preinfarction:de,ab,ti))	24,792
#2	Search 'heart infarction'/exp OR (myocardial NEXT/1 infarct*):de,ab,ti OR (myocardium NEXT/infarct*):de,ab,ti OR (heart NEXT/1 infarct*):de,ab,ti OR (cardiac NEXT/1 infarct*):de,ab,ti	344,803
#3	Search 'acute coronary syndrome'/exp OR ('acute coronary' NEXT/1 syndrome*): de,ab,ti	47,295
#4	Search #1 OR #2 OR #3	374,317
#5	Search 'protocol compliance'/exp OR 'practice guideline'/exp OR guideline*: de,ab,ti OR protocol*:de,ab,ti AND (adheren*:de,ab,ti OR complian*:de,ab,ti)	56,329
#6	Search #4 AND #5	1911

A.3 CINAHL

Search	Query	Nr. of hits
S1	(MH "Angina, Unstable")	1,758
S2	TI angina OR AB angina OR SU angina	7,817
S3	TI ((unstable OR preinfarction)) OR AB ((unstable OR preinfarction)) OR SU ((unstable OR preinfarction))	6,944
S4	(TI (unstable OR preinfarction) OR AB (unstable OR preinfarction) OR SU (unstable OR preinfarction)) AND (S2 AND S3)	2,489
S5	S1 OR S4	3,248

A.3 CINAHL

Search	Query	Nr. of hits
S6	(MH "Myocardial Infarction+") OR TI (("Myocardial infarct*" OR "Myocardium infarct*" OR "heart infarct*" OR "cardiac infarct*")) OR AB (("Myocardial infarct*" OR "Myocardium infarct*" OR "heart infarct*" OR "cardiac infarct*")) OR SU (("Myocardial infarct*" OR "Myocardium infarct*" OR "heart infarct*" OR "cardiac infarct*"))	39,768
S		6,654
S7	S5 OR S6 OR S7	6,654
S8	(MH "Guideline Adherence")	46,962
S9	TI ((guideline* OR protocol*)) OR AB ((guideline* OR protocol*)) OR SU ((guideline* OR protocol*))	8,688
S10	TI ((adheren* OR complian*)) OR AB ((adheren* OR complian*)) OR SU ((adheren* OR complian*))	159,823
S11	S5 OR S6 OR S7	76,633
S12	S10 AND S11	17,615
S13	S9 OR S12	9,290
S14	S8 AND S13	353

A.4 Cochrane library

Search	Query	Nr. of hits
#1	Angina:ti,ab,kw AND (unstable:ti,ab,kw OR preinfarction:ti,ab,kw)	2,455
#2	"Myocardial infarct*":ti,ab,kw OR "Myocardium infarct*":ti,ab,kw OR "heart infarct*":ti,ab,kw OR "cardiac infarct*":ti,ab,kw	19,235
#3	acute coronary syndrome*:ti,ab,kw	3,365
#4	#1 or #2 or #3	21,664
#5	(guideline*:ti,ab,kw OR protocol*:ti,ab,kw) AND (adheren*:ti,ab,kw OR complian*:ti,ab,kw)	5920
#6	#4 and #5	119

3

Monitoring guideline adherence in ACS: study protocol

Design of a multicentre study regarding guideline adherence in the management of acute coronary syndrome in hospitals

This chapter has been adapted from: Tra J, Engel J, Van der Wulp I, De Bruijne MC, Wagner C. Monitoring guideline adherence in the management of acute coronary syndromes in hospitals: design of a multicenter study. Netherlands Heart Journal 2014;22(7-8):346-353.

Abstract

Background

Increasing guideline adherence in the management of acute coronary syndrome (ACS) in hospitals potentially reduces heart failure and mortality. Therefore, an expert panel identified three guideline recommendations as the most important aims for improvement in ACS care, i.e. timely invasive treatment, use of risk scoring instruments and prescription of secondary prevention medication at discharge.

Aims

This study aims to evaluate in-hospital guideline adherence in the care of patients diagnosed with ACS and to identify associated factors.

Methods

The study has a cross-sectional design. Data are being collected in 13 hospitals in the Netherlands by means of retrospective chart review of patients discharged in 2012 with a diagnosis of ACS. The primary outcomes will be the percentages of patients receiving timely invasive treatment, with a documented cardiac risk score, and with a prescription of the guideline-recommended discharge medication. In addition, factors associated with guideline adherence will be studied using generalized linear (mixed) models.

Discussion

This study is exploring guideline adherence in Dutch hospitals in the management of patients diagnosed with ACS, using a data source universally available in hospitals. The results of this study can be informative for professionals involved in ACS care as they facilitate targeted improvement efforts.

3.1 Background

Patients diagnosed with an acute coronary syndrome (ACS) have a high risk of dying from their condition. Mortality rates differ for the three clinical manifestations of ACS: ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI) and unstable angina (UA) [1]. The symptoms of ACS are usually caused by the same pathophysiological mechanism, i.e. coronary stenosis. However, the differences in severity of coronary stenosis and mortality have led to differences in the management of ACS [2,3].

Improved management strategies for patients diagnosed with ACS have led to a decrease in mortality rates in the past years [4-6]. For patients with STEMI the strategy progressed from acute pharmacological intervention (thrombolysis) to immediate percutaneous coronary intervention (PCI) [7]. In the management of NSTEMI and UA patients, risk scoring instruments were developed and implemented to estimate patients' future risk of major adverse cardiac events in order to weigh the risks and benefits of invasive treatment [8]. Independent of the type of ACS, prescribing secondary prevention medication further reduces morbidity and prevents additional episodes of ACS [9]. Using the aforementioned strategies increases patients' chances of survival [10,11], and these strategies are therefore incorporated in international cardiology guidelines [12,13].

However, previous studies reported that not all patients are treated according to these guideline-recommended strategies [14,15]. For example, patients with higher age, female sex, prior heart failure, renal insufficiency or coronary artery bypass graft (CABG) surgery during admission were less likely to receive guideline-recommended discharge medication [16]. Also, variation in guideline adherence between hospitals has been reported [10]. To identify room for improvement in the management of ACS, it is imperative to monitor guideline adherence and to identify associated factors.

The objective of this study is therefore to determine the degree of ACS guideline adherence in Dutch hospitals. A Dutch expert panel identified timely invasive treatment, use of cardiac risk scoring instruments and prescribing guideline-recommended discharge medication as the most important aims for improvement in ACS care. A secondary objective of this study is to explore patient and hospital characteristics associated with guideline adherence. In the present paper the design of the study will be outlined.

3.1.1 Research questions

To what degree are:

1. patients diagnosed with STEMI treated with PCI within 90 minutes of first (para) medical contact?
2. cardiac risk scoring instruments used in the management of patients diagnosed with NSTEMI/UA?
3. the recommended medicines for secondary prevention prescribed to patients diagnosed with ACS at discharge from the hospital?

Additionally, what patient and hospital characteristics are associated with guideline adherence?

3.2 Methods

3.2.1 Design

The study has a cross-sectional design.

3.2.2 Setting

In the Netherlands 33 out of the 91 hospitals offer PCI, of which 16 also provide CABG surgery. The three guideline recommendations monitored in the present study were identified from the European Society of Cardiology guidelines by an expert panel consisting of cardiologists, an emergency department medical resident, an intensive care / cardiac care nurse and health care scientists. Adherence to these three recommendations is measured over 2012, the last year of a national quality improvement program. The program aims to decrease in-hospital mortality caused by ten high-risk patient safety threats [17], including ACS.

3.2.3 Selection of hospitals

The study is being conducted in 13 hospitals, selected by means of a multi-stage random sampling procedure. Initially six PCI-capable and six non-PCI-capable hospitals with a cardiology department were randomly selected from a pool of 40 randomly selected hospitals. Three PCI-capable hospitals declined participation, for which three additional PCI-capable hospitals were selected. Because the number of STEMI patients was relatively small, an additional PCI-capable hospital was selected. The hospitals are located in 7 of the 12 Dutch provinces, with bed capacities ranging between 200 and 1200 beds (Table 3.1).

Table 3.1 Characteristics of hospitals included in the study

Hospital ID	1	2	3	4	5	6	7	8	9	10	11	12	13
Type	Gen	Gen	Gen	Teach	Teach	Gen	Teach	Teach	Teach	Acad	Teach	Teach	Acad
Bed capacity	200-400	200-400	200-400	400-600	400-600	800-1000	600-800	600-800	600-800	600-800	1000-1200	800-1000	800-1000
PCI	No	No	No	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
CABG	No	No	No	No	No	No	No	No	Yes	Yes	Yes	Yes	Yes

Due to privacy reasons, bed capacity is categorized and the province per hospital is not included.
Gen general hospital; teach tertiary teaching hospital; Acad academic hospital; PCI percutaneous coronary intervention; CABG coronary artery bypass grafting surgery

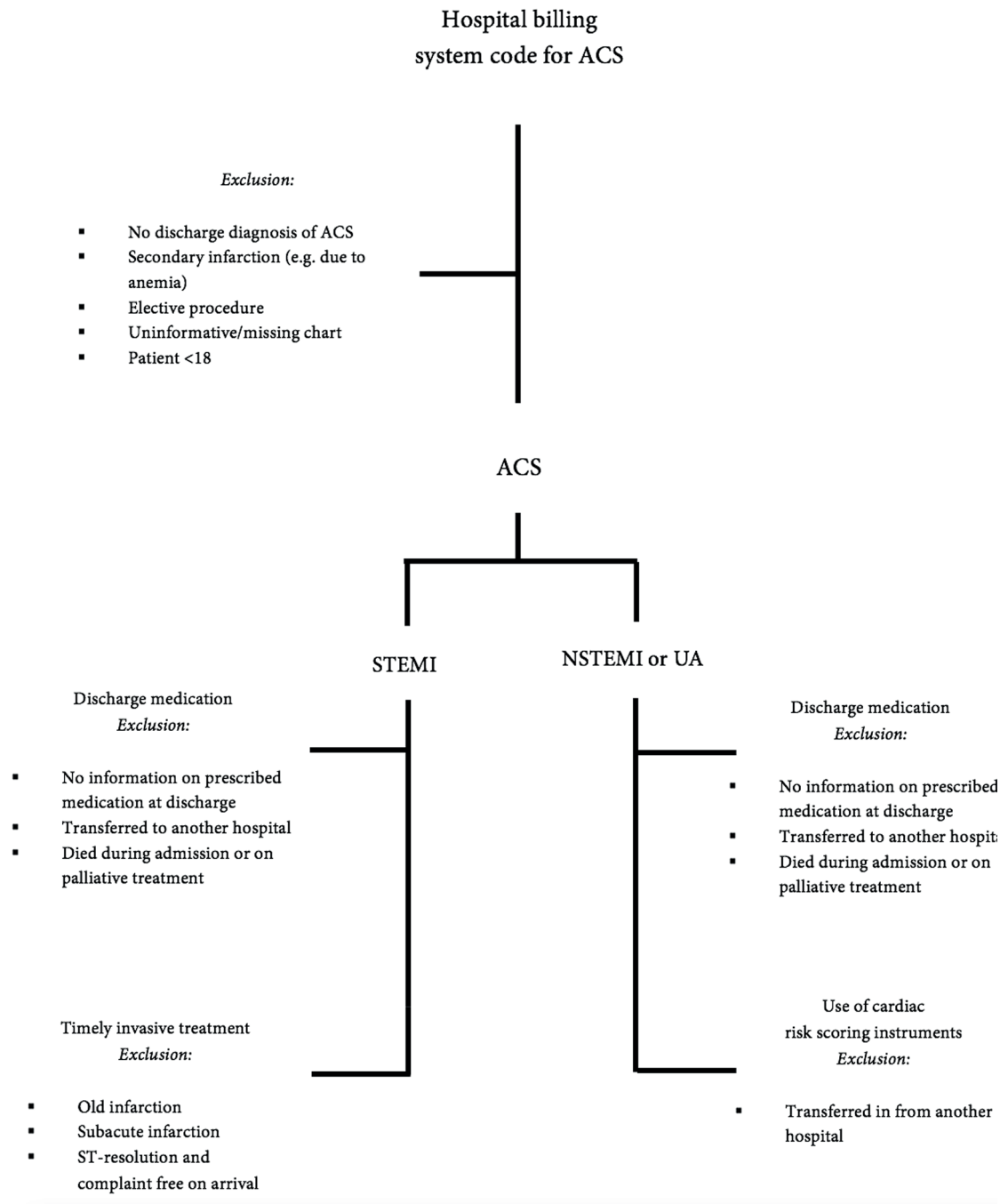

Figure 3.1 Flow chart of the selection of patient charts. *ACS* acute coronary syndrome; *STEMI* ST-segment elevation myocardial infarction; *NSTEMI* non-ST-segment elevation myocardial infarction; *UA* unstable angina

3.2.4 Data collection

The data are collected by means of retrospective chart review of electronic and/or paper-based medical, nursing and catheterization laboratory charts of patients discharged between January 1st and December 31st 2012. Monthly, potential study charts are selected from the hospital billing system using diagnosis-treatment combination codes. Charts of patients discharged with a confirmed diagnosis of ACS (indicated in the discharge letter) are considered for inclusion (Figure 3.1). When the discharge diagnosis is unclear, the chart is discussed with a cardiologist or other attending physician working in the field of cardiology. Charts of patients without a discharge diagnosis of ACS, a secondary ACS (e.g. due to anaemia), elective procedures, missing or uninformative charts, and charts of patients under the age of 18 years are excluded from the study. Moreover, additional exclusion criteria were defined for each process indicator separately. For timely invasive treatment, charts of STEMI patients not going for acute PCI are excluded. For use of risk scoring instruments, charts of patients transferred from another hospital are excluded. For discharge medication, charts of patients who were transferred to another hospital, patients who died during their admission or received palliative treatment are excluded.

3.2.5 Study outcomes

The study has three main outcome measures. First, the percentage of STEMI patients in which the PCI procedure started within 90 minutes from first (para)medical contact. Second, the percentage of NSTEMI or UA patients where use of a validated risk scoring instrument was documented. Finally, the percentage of ACS patients with a prescription of the recommended discharge medication, documentation of a contraindication or other reason for not receiving the recommended medication. Additionally, patient and hospital characteristics associated with guideline adherence will be identified.

3.2.6 Recorded variables

From all charts, the following information is abstracted: demographic and clinical information including gender, age, cardiac history, risk factors, biomarker values, electrocardiogram findings, resuscitation, heart failure, cardiogenic shock on arrival and month of discharge (Table 3.2).

Table 3.2 Information recorded for all ACS patients

General information	**Cardiac rehabilitation (yes/no)**
Gender	Enlistment for cardiac rehabilitation
Date of birth	
Admission date and time	
Symptoms	
Discharge date	
Discharge status (discharged, deceased, unknown)	
Vital functions	**History of cardiac disease (yes/no)**
Cardiogenic shock (yes/no)	Coronary vascular disease
Heart failure (yes/no)	Peripheral vascular disease
Resuscitation (yes/no)	(Unstable) angina pectoris
Blood pressure on arrival (mmHg)	Acute myocardial infarction
Heart rate (beats per minute)	Coronary artery bypass grafting, year_____
Electrocardiogram date and time	Percutaneous coronary intervention, year:_____
Electrocardiogram interpretation	Intervention/acute myocardial infarction <6months
Biomarkers values (troponin, creatinin kinase (CK), creatinin kinase-muscle/brain (CK-MB), creatinine)	
Risk factors (yes/no)	**Risk factors (yes/no) (continued)**
Diabetes mellitus	Elevated cholesterol levels (statin use in history, hyper-
Hypertension	Lipidaemia, hypercholesterolaemia)
Kidney failure	Obesity (body mass index >30 kg/m2)
Chronic heart failure	Coronary stenosis >50% (in history)
Positive family history	Age >70 years
Smoker	Male sex
Previous smoker	Aspirin use (<7 days)

Table 3.2 Information recorded for all ACS patients (continued)

Discharge medication	**Contraindications (yes/no) (continued)**
Acetylsalicylic acid	*Statin*
Thienopyridine	Liver function impairment
Statin	Renal impairment
Beta blocker	Other:_____
Angiotensin-converting enzyme inhibitor	*Beta blocker*
Contraindications (yes/no)	Sick-sinus syndrome
Acetylsalicylic acid	2nd and 3rd degree AV block (ECG)
Coagulation defect	Hypotension
Active peptic ulcer (ulcus pepticum)	Cardiogenic shock
Stroke (bleeding)	Sinus bradycardia
Liver failure	Unstable or untreated heart failure
Kidney failure	Pheochromocytoma
Allergy/oversensitivity	Bronchial asthma (anamnesis)
Treatment with anticoagulant medication	Severe peripheral circulation defects
G6PD-deficiency	Metabolic acidosis
Other:_____	Pulmonary hypertension
Thienopyridine	Kidney failure
Transient ischemic attack/ cerebrovascular accident	Liver failure
Active peptic ulcer (ulcer pepticum)	Myocardial infarction with heart frequency <45, P-Q>0.24, systolic blood pressure <100
Liver failure	*Angiotensin-converting enzyme inhibitor*
Pathological bleeding (from ulcus pepticum or intracranial	Kidney failure
Other:_____	Other:_____

ACS acute coronary syndrome

In addition, for the timely invasive treatment indicator, the following variables are recorded: routing of the patient, type of first (para)medical contact, place of first electrocardiogram, type of treatment, and the dates and times of first (para)medical contact, first (ambulance/ general practitioner) electrocardiogram and sheath insertion (start of PCI) (Table 3.3). To evaluate cardiac risk score adherence, application of a validated risk scoring instrument (e.g. GRACE [18;19], TIMI [20], FRISC [21], HEART [22] and PURSUIT [8]), type of instrument, risk score outcome, date of application, and type of treatment are recorded (Table 3.4). Finally, for discharge medication, prescription of acetylsalicylic acid, thienopyridine, statin, beta blocker and angiotensin-converting enzyme (ACE) inhibitor and contraindications or other reasons for not prescribing all or some of the medication are recorded (Table 3.1). Contraindications were derived from an annually updated database containing information about all medication registered in the Netherlands [23].

Table 3.3 Additional recorded variables for STEMI patients

General information
Routing out-of-hospital
Type of treatment (pharmacological, acute PCI, non-acute percutaneous coronary intervention, CABG)
Discipline of first (para)medical contact
Discipline of first electrocardiogram
Number of diseased vessels
Location of stenosis
Time variables
Symptom onset
First (para)medical contact
First electrocardiogram
Sheath insertion
First balloon inflation or thrombus aspiration

CABG coronary artery bypass graft surgery; PCI percutaneous coronary intervention; STEMI ST-segment elevation myocardial infarction

Table 3.4 Additional recorded variables for NSTEMI and UA patients

General information	**Risk score**
Routing in-hospital	Use of validated risk score (yes/no)
Catheterization (yes/no)	Date of application
Type of treatment (pharmacological, PCI, CABG, unknown, other)	Type of instrument(s)
	Risk score outcome
	Risk score outcome classification
	Additional diagnostics

CABG coronary artery bypass graft surgery; NSTEMI non-ST-segment elevation myocardial infarction; PCI percutaneous coronary intervention; STEMI ST-segment elevation myocardial infarction; UA unstable angina

3.2.7 Abstraction of data

All data are collected on standard case report forms. Variables are defined in codebooks. Two researchers (JT & JE) developed the codebooks and case report forms based on the European Society of Cardiology guidelines. The case report forms were discussed within the research group, tested in two pilot measurements and adjusted accordingly. The data are collected by six chart abstractors who were introduced to the subject of ACS and instructed in the chart review procedures by JT and JE. Chart reviews were supervised until the quality of the chart reviews was satisfactory. The data are entered into a database using a data entry program with fixed entry fields (BLAISE version 4.7, Statistics Netherlands) and compared with the original case report form by a second researcher.

To ensure reliability of the data and to assess the quality of the codebook, a sample of charts (5-10%) is independently screened again by one of the five other chart abstractors. The two case report forms are compared, and differences are discussed until consensus is reached. If necessary, changes are made in the original case report form. The reliability between the chart abstractors will be calculated by means of the percentage of agreement for each variable.

3.2.8 Statistical analyses

Missing data

Missing data patterns will be analysed by means of missing value analyses. Depending on the pattern [24], missing values will be imputed by means of a single imputation (missing completely at random) or multiple imputation procedure (missing at random) [25].

Descriptive statistics

The degree of adherence to the three process indicators will be presented by descriptive statistics. Associations of patient and hospital characteristics with guideline adherence are studied in separate analyses.

Timely invasive treatment

The time to PCI in minutes will be entered as a continuous dependent variable in a generalized linear model taking into account its distribution, as time variables are generally not normally distributed. In univariate analyses, associations of the independent variables, i.e. patient and admission characteristics, are studied. To account for clustering of patient data within hospitals, the variable 'hospital' and its significant interactions with any other of the predictor variables will be entered as a covariate in all univariate models [26]. This is because the hospital sample size (7 PCI-capable hospitals) is considered small for multilevel regression analysis27. All variables and interactions significantly ($p \leq 0.05$) associated with

the time to PCI will be included in the multiple generalized linear model. Furthermore, to minimize the probability of making a type II error, all non-significant variables from the univariate models will be added to the multiple generalized linear model one by one. Significant variables ($p \leq 0.05$) will be added to the final model.

Use of risk scoring instruments

Associations of independent variables with the use of cardiac risk scoring instruments will be studied by means of a generalized linear mixed model (GLMM). In the analysis the binary dependent variable will be the use of a validated risk score instrument. Independent variables will be patient characteristics, hospital characteristics and month of discharge. To account for clustering of the data, the model will comprise random effects for hospitals. First, independent variables will be tested separately correcting for the random hospital effects. Second, all independent variables with a significance level below $p \leq 0.15$ will be selected. Next, pairs of selected independent variables will be tested jointly. Last, all significant ($p \leq 0.05$) variables from the previous steps will be included in the final multivariable model. This final step also comprises a cautious consideration of significant ($p \leq 0.05$) interaction terms.

Discharge medication

Associations of independent variables with the prescription of the recommended discharge medication will be studied by means of GLMM. In these analyses, prescription of the five guideline-recommended medicines or documentation of contraindications (yes/no) will be the binary dependent variable. The effects of the independent variables including patient, hospital and discharge characteristics will be tested in univariate analyses. All variables with a significant association ($p \leq 0.05$) with the dependent variable will be included in a multivariable model. To account for the effects of collinearity, all variables not significantly related to prescription of the recommended discharge medication in the univariate models will be added to the multivariable generalized linear mixed model one by one. Interactions will be tested and added to the multivariable model in case of a significant effect. In all models, hospital will be entered as a random effect variable to account for clustering of the data. As not all medicines are indicated for all patients with ACS according to the European Society of Cardiology guidelines (e.g. ACE-inhibitors are recommended for all patients with ACS, but only indicated for those patients with a reduced cardiac function), additional models will be created to analyse the effects of patient and hospital characteristics on the prescription of ≤3 and ≥4 medicines or documentation of a contraindication.

Software

The data will be analysed in IBM SPSS Statistics (version 20 for Windows) and R (version 3.0.0 for Windows).

3.2.9 Ethical approval and confidentiality

The study protocol was approved by the medical ethics review committee of the VU University Medical Center. To protect patients' and hospitals' privacy, they are assigned a unique observation code. All data are stored on a password protected network server of the VU University Medical Center, to which only the participating researchers have access. All chart abstractors signed a confidentiality agreement and the study was registered with the Dutch Data Protection Agency.

3.3 Discussion

This paper describes the design of a study of the quality of Dutch ACS care by evaluating the degree to which hospitals adhere to three key quality indicators from (inter)national guidelines and by exploring factors associated with guideline adherence.

Previous North American studies that monitored guideline adherence have successfully identified associated factors [10,16,28], after which targeted quality improvement efforts could be applied. These efforts increased the likelihood that patients were treated on time with PCI [29], risk scores were documented [30] and the recommended discharge medication was prescribed [31]. Therefore the monitoring of guideline adherence as the foundation for targeted quality improvement efforts seems promising.

The three guideline recommendations evaluated in this study were selected from the European Society of Cardiology guidelines [12,13], but are also included in other (inter) national guidelines [32-34]. The methods used in this study can be applied to evaluate the process of ACS care in other countries, especially in countries where large, national registries of guideline adherence are lacking.

3.3.1 Potential limitations

In designing the study, several limitations have to be taken into account. First, the documented information in the charts and variability between the chart abstractors may affect the reliability of the data. This will be reduced by using standardized case report forms, a codebook and by interim reliability checks of the data. Second, using the diagnosis in the discharge letter as inclusion criterion may not be as reliable as applying our own diagnostic criteria. However, it was considered important to take into account the interpretation of the treating physician at the time of hospitalization of the patient. Third, the presence of researchers on site, and quarterly feedback from the national quality improvement program might influence hospitals' performance on the outcomes. However, in a report on the evaluation of the quality improvement program the effect of this national intervention was

limited [35]. Finally, the selection of hospitals and patients could not be performed completely randomly due to practical limitations. However, the hospitals included in this study were geographically spread over the country, thereby limiting the influence of potential regional variation in guideline adherence. Additionally the outcomes of this study are corrected for the influence of individual hospitals in the statistical models.

3.4 Conclusion

Evidence-based guidelines are of vital importance in safely and effectively treating patients diagnosed with ACS. The results of this study will provide insight into the degree of guideline adherence in Dutch hospitals for the management of patients with ACS and identify room for further improvement. Furthermore, patient and hospital characteristics associated with guideline adherence will be identified, which may facilitate targeted improvement strategies.

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4

Cardiac risk score use in NST-ACS: a patient chart review study

A cross-sectional multicentre study of cardiac risk score use in the management of unstable angina and non-ST-elevation myocardial infarction

This chapter has been adapted from: Engel J, Van der Wulp I, De Bruijne MC, Wagner C. A cross-sectional multicentre study of cardiac risk score use in the management of unstable angina and non-ST-elevation myocardial infarction. BMJ Open 2015;5:e008523.

Abstract

Background

Quantitative risk assessment in unstable angina (UA) and non-ST-elevation myocardial infarction (NSTEMI), by using cardiac risk scores, is recommended in international guidelines. However, a gap between recommended care and actual practice exists, as these instruments seem underused in practice. The present study aimed to determine the extent of cardiac risk score use and to study factors associated with lower or higher cardiac risk score use.

Methods

A retrospective chart review of 1788 charts of UA and NSTEMI patients, discharged in 2012, from thirteen hospitals throughout the Netherlands.

Primary and secondary outcomes: The extent of cardiac risk score use reflected in a documented risk score outcome in the patient's chart. Factors associated with cardiac risk score use determined by generalized linear mixed models.

Results

In 57% (n=1019) of the charts, physicians documented the use of a cardiac risk score. Substantial variation between hospitals was observed (16.7% – 87%), although this variation could not be explained by the presence of on-site revascularization facilities or a hospitals' teaching status. Obese patients (OR=1.49; CI 95% 1.03 to 2.15) and former smokers (OR=1.56; CI 95% 1.15 to 2.11) were more likely to have a cardiac risk score documented. Risk scores were less likely to be used among patients diagnosed with unstable angina (OR=0.60; CI 95% 0.46 to 0.77), in-hospital resuscitation (OR=0.23; CI 95% 0.09 to 0.64), in-hospital heart failure (OR=0.46; CI 95% 0.27to 0.76) or tachycardia (OR=0.45; CI 95% 0.26 to 0.75).

Conclusions

Despite recommendations in cardiac guidelines, the use of cardiac risk scores has not been fully implemented in Dutch practice. A substantial number of patients did not have a cardiac risk score documented in their chart. Strategies to improve cardiac risk score use should pay special attention to patient groups in which risk scores were less often documented, as these patients may currently be undertreated.

4.1 Background

In the past decade mortality rates in acute coronary syndromes, including unstable angina (UA) and non-ST-elevation myocardial infarction (NSTEMI), decreased significantly due to substantial improvements in treatment possibilities [1,2]. Despite these advancements, these conditions still account for a large part of the annual deaths worldwide and are expected to be the leading cause of death and to account for the largest disease burden worldwide by 2020-2030 [3-5]. Part of these deaths may be prevented, as it has previously been reported that a substantial number of patients were not treated according to the current standards of care [6-8]. Patients with diabetes mellitus, renal insufficiency, signs of heart failure and patients aged 75 years or older were often neglected guideline recommended care [6]. On the other hand, patients presenting to academic hospitals and to hospitals with revascularisation facilities on-site (e.g. percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG)) were more often treated in accordance to the guidelines [7,9]. Patients diagnosed with UA or NSTEMI can be treated with medication or invasive procedures such as PCI or CABG. According to international cardiac guidelines the decision to treat such patients with one or the other may be made on the basis of a quantitative assessment of the patient's risk of re-infarction or death [10-12]. To assist clinicians in identifying patients at high risk of adverse cardiac events that would benefit most from invasive therapies, several instruments have been developed [10-12]. The GRACE (Global Registry of Acute Coronary Events) [13,14], TIMI (Thrombolysis in Myocardial Infarction) [15], FRISC (fast revascularisation in instability in coronary disease) [16], PURSUIT (Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin) [17] and HEART risk scores [18] are examples of validated cardiac risk scoring instruments. In estimating risk, these instruments incorporate and combine several diagnostic elements including a patients' history, biomarkers and ECG findings, and can be used in the emergency department or coronary care unit. The predictive validity of these instruments was reported to be good [16,19,20]. Previous research found that cardiac risk scores were effective in identifying patients at high risk for cardiac events [21,22]. However, a gap between recommended care in the guidelines and actual practice seems to exist, as it has been suggested before that cardiac risk scores are not routinely used in clinical practice [21,23,24]. This possibly contributes to perpetuating the "treatment risk paradox", in which patients with low risk of adverse cardiac events, opposite to cardiac guideline recommendations, were more likely to receive invasive cardiac treatment compared with high-risk patients [6,25-30]. Prior to creating future improvement initiatives aimed to increase cardiac risk score use, knowledge about the extent of this gap and associated factors is necessary. The present study, therefore, aimed to determine the extent of cardiac risk score use in Dutch clinical practice and to study factors associated with lower or higher cardiac risk score use.

4.2 Methods

This study concerns a cross-sectional multicentre study. A detailed description of the study protocol has been published previously [31]. The study protocol was reviewed and approved by the medical ethical committee of the VU University Medical Centre Amsterdam. Where required, approval from hospitals' local ethics board was obtained.

4.2.1 Setting

In 2008 all hospitals in the Netherlands committed themselves to the implementation of a quality improvement programme aimed to enhance patient safety in Dutch hospitals. The programme comprised several themes, including the theme 'Optimal care for Acute Coronary Syndromes' which, among other things, aimed to increase the application of cardiac risk scores in clinical practice [32]. A random selection of 40 hospitals participated voluntarily in the evaluation of the nationwide quality improvement programme. By a multistage random sampling procedure, initially 12 hospitals were selected from the pool of 40 hospitals to participate in the current study (i.e., evaluation of cardiac risk score use). Three PCI-capable hospitals declined participation, for which three additional PCI-capable hospitals were selected. Additionally, one hospital was selected to obtain optimal diversity in on-site revascularisation facilities and teaching status. The final sample consisted of 13 hospitals, of which 2 university hospitals, 7 tertiary teaching hospitals, and 4 general hospitals. Bed capacity in the hospitals varied between 200 and 1200 beds.

4.2.2 Data collection

The primary study outcome was the extent to which cardiac risk scores were used in the management of patients with UA and NSTEMI reflected in a documented risk score outcome in the patient's chart. Data were collected monthly by means of retrospective chart review.

Potentially eligible charts were selected from the hospitals' billing system based on diagnostic-related group codes for UA and NSTEMI. All patients discharged in 2012, 18 years or older, with a diagnosis of UA or NSTEMI (as confirmed in the discharge letter) were considered for inclusion. Charts of patients who were transferred in from another hospital were excluded, as these patients were initially treated elsewhere and therefore the necessary data could not be obtained. In addition, charts of patients who provided insufficient information regarding the discharge diagnosis, who were hospitalized for an elective procedure, or who had an underlying illness or condition, other than a coronary stenosis, causing UA or NSTEMI (e.g. anaemia) were excluded.

Charts of patients were selected per month in chronological order of discharge, until the screening capacity of the chart abstractors was reached. Charts of potentially eligible patients were manually reviewed to confirm a discharge diagnosis of UA or NSTEMI. In case a

patient's final discharge diagnosis was unclear, a physician of the cardiology department was consulted. The following patient-related and hospital-related information was registered on standardized data extraction forms: demographic characteristics, cardiac history, presence of cardiac risk factors, presenting symptoms, biochemical and ECG findings and treatment practices. In addition, information regarding cardiac risk score use was registered, including the use of a validated risk score (yes/no), date of application, type of risk score used and risk score outcome and classification. Besides patient-related information, the following hospital factors were registered: teaching status (yes/no) and the presence of onsite revascularisation facilities.

The data were entered into a database using fixed entry fields (BLAISE version 4.7, Statistics Netherlands) and data reliability checks were conducted. To ensure reliable data extraction, more than 5% (103/1933) of the charts were screened by two chart abstractors independently. The total percentage of agreement between these abstractors was 95.1%, and ranged for the variables of interest (Table 4.1) between 80.6% (ECG findings) and 100% (gender), indicating good to excellent data reliability.

Table 4.1 Independent variables in Generalized Linear Mixed Model

Patient characteristics		**Hospital characteristics**
Demographics	*Presenting factors*	• Presence of revascularization options
• Age	• Heart rate	• Teaching status
• Gender	• Systolic blood pressure	
Discharge diagnosis	• Resuscitation at admission	
• UA	• Cardiogenic shock	
• NSTEMI	• In-hospital heart failure	
Risk factors	• ST deviations on ECG	
• Diabetes mellitus	*Cardiac history*	
• Hypertension	• Coronary artery disease	
• Renal failure	• Peripheral vascular disease	
• Chronic heart failure	• (Unstable) angina pectoris	
• Positive family history	• Acute myocardial infarction	
• Smoking	• Previous CABG	
• Former smoker	• Previous PCI	
• Hypercholesterolemia*	• Revascularization/AMI <6 months	
• Obesity (BMI > 30)		
• Coronary stenosis ≥50% (in history)		

Abbreviations: ECG, electrocardiogram; UA, unstable angina; NSTEMI, non-ST-elevation myocardial infarction; CABG, Coronary artery bypass graft surgery; PCI, Percutaneous coronary intervention; AMI, acute myocardial infarction; BMI, body mass index. *Defined as statin use prior to admission, or described in patients history (elevated cholesterol levels, hyperlipidaemia or hypercholesterolemia).

4.2.3 Missing data

In total, 1.5% of the values in the dataset were missing, ranging from 0.1% to 22% per variable. Eleven variables had no missing values, including cardiac risk score use. Despite the small amount of missing data and the spread of missing data in the dataset, a complete case analysis would have led to a large loss of information and power. Therefore, missing values were imputed using a multiple imputation procedure following the approach of van Buuren and Groothuis-Oudshoorn [33], resulting in five imputed datasets. In imputing missing values it was assumed that the data were missing at random. The estimated values were corrected for the variables 'hospital' and 'cardiac risk score use' as these variables were of primary interest in the analyses. By means of the Kolmogorov-Smirnov test, and density and residual plots, it was determined whether the missing at random assumption was sustainable and the imputed values were plausible. In addition, a sensitivity analysis was conducted by comparing the results from the analyses of the imputed data with the results of a complete case analysis. Between these models, only small differences were found. The missing value analyses and their imputations were conducted in R (version 3.0.2 for Microsoft Windows) using the MICE package [33,34].

4.2.4 Data analysis

Sample characteristics were calculated using descriptive statistics, and included frequencies and percentages for categorical variables, and means and SDs for continuous variables. Associations of independent variables (Table 4.1) with the use of cardiac risk scores (yes/no) were studied with a generalised linear mixed model (GLMM), taking into account the clustering of data within hospitals35. ORs, that are based on median probabilities over hospitals for cardiac risk score use, are presented. To facilitate interpretation, relevant explanatory variables were transformed into categorical variables (i.e., age, heart rate and systolic blood pressure). Furthermore, month of discharge was represented by a categorical variable with 12 levels in every model, to account for the fact that chart abstractors were present on hospital departments to abstract data. In univariate analyses, associations between cardiac risk score use and the independent variables were tested. All variables with a significance level of $p \leq 0.15$ were entered in a multivariable model. Variables significantly associated ($p \leq 0.05$) with cardiac risk score use in the multivariable model were considered important in predicting risk score adherence. In addition, based on previous literature two factor interactions with on-site revascularization options, teaching status, age and gender were tested. All analyses were conducted in R for windows (version 3.0.2) using the package lme4 on pooled data of five imputed data sets [34]. The script of the pool function in MICE was rewritten for pooling GLMM models.

4.3 Results

4.3.1 Study population

A total of 1933 charts of patients with a confirmed diagnosis of UA or NSTEMI were screened. Of these, 145 (7.5%) were excluded from the study as these concerned patients transferred from one hospital to another, leaving 1788 patients for further analysis (Figure 4.1). The majority (62.6%) of these patients had a discharge diagnosis of NSTEMI (Table 4.2). Males accounted for 66.9% of the patients, and more than a third (35.9%) of the patients were aged 75 years or older. Three quarters (75.3%) of the total population underwent coronary catheterisation. The average length of hospital stay was 5 days (SD 4.97).

4.3.2 Cardiac risk score use

In 57% of the patient charts, a cardiac risk score was documented, though, substantial variation between hospitals was observed, that is, 16.7-87% (Table 4.3). Six out of the 13 hospitals used more than one risk scoring instrument to calculate a risk score, being the following: GRACE (12/13 hospitals), TIMI (3/13 hospitals), FRISC (1/13 hospitals) and the HEART risk score (6/13 hospitals; Table 4.3). The variance component for the random hospital effect in the GLMM ranged between 1.29 and 1.31 in the five imputed datasets, confirming the great variety between hospitals in the use of cardiac risk scores. When, for instance, the effects for two hospitals are equal to the 5th and 95th centiles of the normal distribution with variance 1.3 for hospital effects, the OR of one hospital relative to the other for cardiac risk score use is 42.6.

In univariate analyses, 15 patient-related factors were significantly ($p \leq 0.15$) associated with cardiac risk score use (Table 4.4). No significant associations with hospital-related factors were found (teaching status p=0.25, on-site revascularisation facilities p=0.67). In multivariable analyses, patients with obesity (OR=1.49; 95%CI= 1.03-2.15; p=0.04) and former smokers (OR=1.56; 95% CI=1.15-2.11; $p \leq 0.01$) were more likely to have a cardiac risk score documented. Conversely patients with UA (OR=0.60; 95% CI=0.46-0.77; $p \leq 0.01$), in-hospital heart failure (OR=0.46; 95% CI=0.27-0.76; $p \leq 0.01$), tachycardia (OR=0.45; 95% CI=0.26-0.75; $p \leq 0.01$) or who had been resuscitated at admission (OR=0.23; 95% CI=0.09-0.64; $p \leq 0.01$) were less likely to have a cardiac risk score documented (Table 4.4).

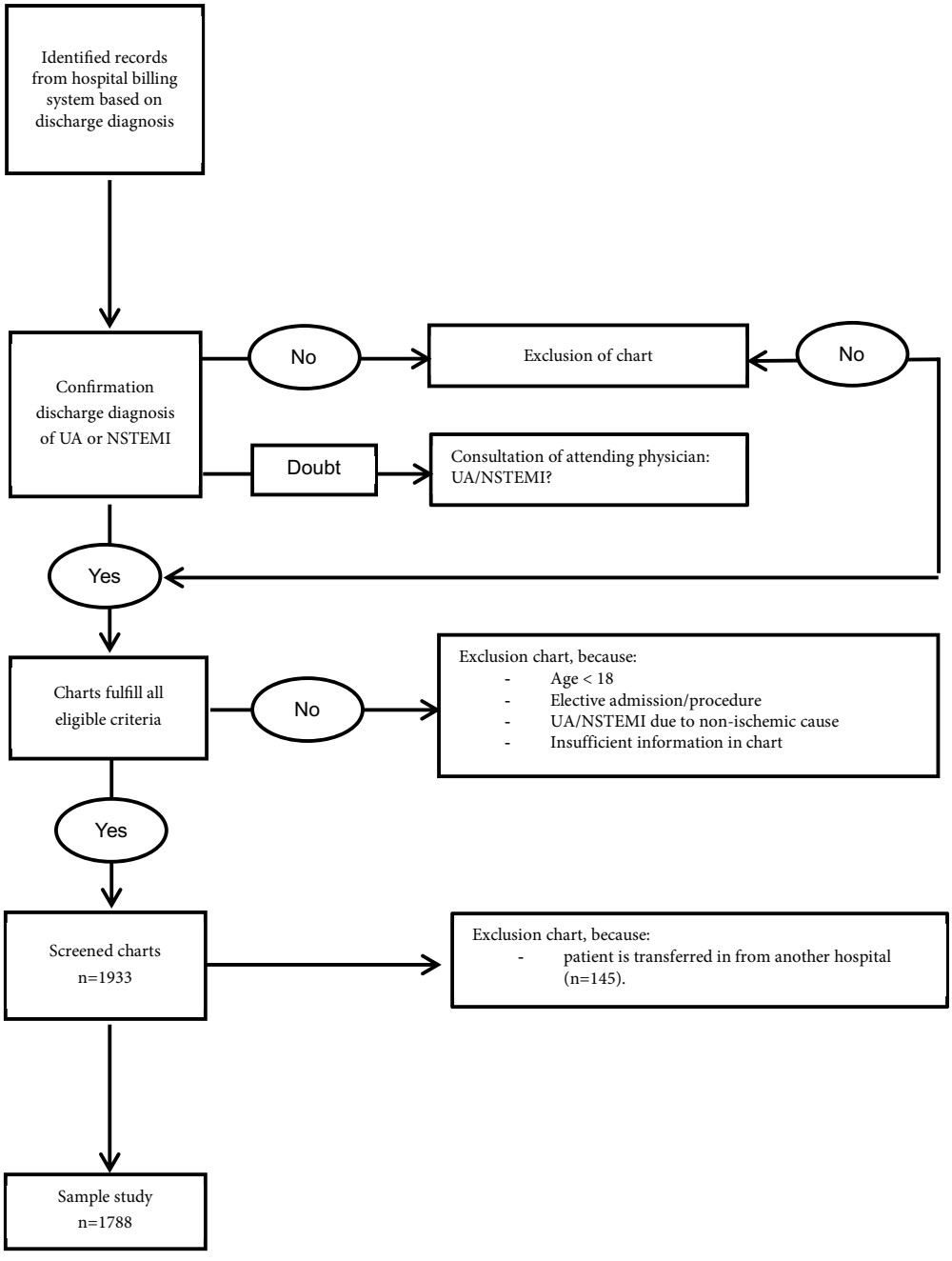

Figure 4.1 Inclusion and exclusion procedure of chart selection and screening

Table 4.2 Baseline characteristics (pooled data)

Baseline characteristics (n= 1788)	**n (%)†**
Age (<75 years)	1146 (64.1)
Gender (male)	1196 (66.9)
Discharge diagnoses (NSTEMI)	1119 (62.6)
Length of hospital stay (days) (mean ± SD)	5 ± 4.97
Systolic blood pressure (mmHg)	
High (≥ 160)	552 (30.9)
Normal to slightly elevated (81-159)	1236 (69.1)
Low (≤ 80)	0 (0)
Heart rate (bpm)	
Tachycardia (≥ 110)	103 (5.8)
Normal (51-109)	1634 (91.4)
Bradycardia (≤ 50)	51 (2.8)
Resuscitation at admission	33 (1.9)
Cardiogenic shock	7 (0.4)
In-hospital heart failure	103 (5.8)
ST deviations on electrocardiogram	810 (45.3)
History of coronary artery disease	252 (14.1)
History of peripheral vascular disease	131 (7.3)
Previous (U)A	432 (24.1)
Previous MI	499 (27.9)
Previous PCI	523 (29.3)
Previous CABG	289 (16.2)
MI or PCI/CABG 6 months prior to admission	125 (7)
Diabetes mellitus	451 (25.2)
Hypertension	936 (52.4)
Renal failure	88 (4.9)
Chronic heart failure	101 (5.7)
Hypercholesterolemia‡	986 (55.1)
Obesity (BMI>30)	203 (11.3)
Smoking	427 (23.9)
Former smoker	350 (19.6)
Coronary stenosis (≥50%)	192 (10.8)
Positive family history	618 (34.6)
Coronary catheterization	1346 (75.3)
Management strategy	
Pharmacological therapy	754 (42.2)
(scheduled) PCI	846 (47.3)
(scheduled) CABG	188 (10.5)

†Data are presented in n(%), unless stated otherwise. ‡ Defined as statin use prior to admission, or described in patients history (elevated cholesterol levels, hyperlipidaemia or hypercholesterolemia).Abbreviations: n.a., not applicable; (U)A, (Unstable)Angina; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; BMI, body mass index.

Table 4.3 Adherence to cardiac risk score use per hospital (pooled data)

Hospital ID†	Teaching Status	PCI/CABG options	Screened charts n‡	Risk score use n (%)[1]	Type of risk score used∞			
					GRACE	TIMI	FRISC	HEART
1	No	No	84	14 (16.7)	X	-	-	-
2	Yes	Yes	109	22 (20.2)	X	X	-	-
3	No	No	110	26 (23.6)	X	-	-	-
4	No	No	171	57 (33.3)	-	-	-	X
5	Yes	Yes	132	46 (34.8)	X	-	-	X
6	Yes	No	53	19 (35.8)	X	-	-	-
7	Yes	Yes	145	79 (54.5)	X	-	X	X
8	Yes	Yes	182	108 (59.3)	X	-	-	X
9	Yes	Yes	96	68 (70.8)	X	-	-	-
10	Yes	Yes	140	107 (76.4)	X	-	-	X
11	Yes	Yes	108	87 (80.6)	X	X	-	X
12	No	No	205	166 (81.0)	X	X	-	-
13	Yes	No	253	220 (87.0)	X	-	-	-
Total	--	--	1788	1019 (57%)	--	--	--	--

† ranging from lowest to highest scoring hospital. ‡ Large variation in screened patient charts per hospital is explained by differences in the amount of monthly admission for UA/NSTEMI.] Risk score use is represented by (one or more) documented risk score outcome(s) in the patient's chart. ∞Several hospitals calculated more than one risk score per patient, using different risk scoring instruments. Abbreviations: CABG, coronary artery bypass grafting; FRISC, fast revascularization in instability in coronary disease; GRACE, global registry of acute coronary events; PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction

Interactions

Besides the interactions with on-site revascularisation options, teaching status, age and gender, it was decided to also test whether interactions with former smoker were present. This, because an unexpected significant association between former smoker and risk score use was found. Significant interactions were found between the variables former smoker and discharge diagnosis (p=0.03), age and previous PCI (p=0.02), age and in-hospital heart failure (p=0.04), age and history of peripheral artery disease (p=0.03), and age and heart rate (p=0.04) (Table 4.5). Looking at the interaction effects with age, it was found that patients aged 75 years or over presenting with a previous PCI had a higher odds of cardiac risk score documentation compared with patients without a previous PCI (OR=1.53; 95% CI=1.00 to 2.34; p=0.05). In contrast, older patients were less likely to have a cardiac risk score documented in case they presented with heart failure (OR=0.29; 95% CI=0.14 to 0.57; p<0.001), with a history of peripheral artery disease (OR=0.47; 95% CI=0.24 to 0.91; p=0.02) or with tachycardia (OR=0.20; 95% CI=0.08 to 0.52; p≤0.001).

Table 4.4 Univariate and multivariable associations between risk score documentation in patient charts and hospital- and patient related factors (pooled data) (n=1788)†

	Univariate associations		**Multivariable associations**	
	OR (95% CI)	*P*	*OR (95% CI)*	*P*
Hospital factors				
Teaching status	2.15 (0.59 – 7.85)	0.25	n.a.	n.a.
On-site revascularization facilities	1.32 (0.38 – 4.60)	0.67	n.a.	n.a.
Patient factors‡				
Discharge diagnosis (*reference* NSTEMI)	0.65 (0.52 – 0.83)	≤0.01**	0.60 (0.46 – 0.77)	≤0.01**
Age (*reference* <75 years)	0.76 (0.61 – 0.96)	0.02*	0.86 (0.67 – 1.11)	0.24
Resuscitation at admission	0.25 (0.10 – 0.67)	≤0.01**	0.23 (0.09 – 0.64)	≤0.01**
In-hospital heart failure	0.38 (0.24 -0.62)	≤0.01**	0.46 (0.27 – 0.76)	≤0.01**
History of coronary artery disease	0.65 (0.47 – 0.89)	≤0.01**	0.87 (0.59 – 1.27)	0.46
History of peripheral artery disease	0.72 (0.47 – 1.09)	0.12	0.81 (0.53 – 1.26)	0.35
Previous (U)A	0.83 (0.64 – 1.07)	0.15	1.00 (0.75 – 1.34)	0.98
Previous MI	0.77 (0.61 – 0.98)	0.03*	0.89 (0.68 – 1.18)	0.43
Previous PCI	0.83 (0.65 – 1.05)	0.13	1.07 (0.80 – 1.43)	0.66
Renal failure	0.54 (0.33 – 0.90)	0.02*	0.72 (0.42 – 1.23)	0.23
Obesity (BMI>30)	1.49 (1.05 – 2.13)	0.03*	1.49 (1.03 – 2.15)	0.04*
Smoking	1.23 (0.95 – 1.60)	0.11	1.16 (0.86 – 1.55)	0.33
Former smoker	1.48 (1.12 – 1.97)	≤0.01**	1.56 (1.15 – 2.11)	≤0.01**
Coronary stenosis (≥50%)	0.65 (0.46 – 0.93)	0.02*	0.81 (0.54 – 1.22)	0.31
Heart rate (bpm) (*reference* Normal)				
Tachycardia	0.46 (0.28 – 0.76)	≤0.01**	0.45 (0.26 – 0.75)	≤0.01**
Bradycardia	0.85 (0.44 – 1.63)	0.62	0.92 (0.46 – 1.86)	0.82

† pooled p-value based on normal approximation. ‡Only variables (patient characteristics) with p ≤ 0.15 in the univariate analyses are presented in this table. Reference category is 'no', unless stated otherwise. *p-value ≤ 0.05; **p-value ≤0.01. Abbreviations: OR, odds ratio; CI, 95% confidence interval; n.a., not applicable; PCI, percutaneous coronary intervention; CABG: coronary artery bypass grafting; (U)A, (Unstable)Angina; MI, myocardial infarction; BMI, body mass index.

Table 4.5 Estimated odds ratio's and 95% confidence intervals for significant (p≤0.05) interactions terms added to multivariable model of GLMM (pooled data) †

Interaction	OR	CI 95%	P-value‡
Former smoker*discharge diagnosis			
Discharge diagnosis (UA vs. NSTEMI) within former smoker (no)	0.52	0.40 – 0.69	<0.001**
Discharge diagnosis (UA vs. NSTEMI) within former smoker (yes)	1.00	0.59 – 1.71	0.98
Former smoker (yes vs. no) within discharge diagnosis (UA)	2.28	1.43 – 3.61	<0.001**
Former smoker (yes vs. no) within discharge diagnosis (NSTEMI)	1.19	0.81 – 1.75	0.38
Age*previous PCI			
Age (≥75 vs. <75 years) within previous PCI (no)	0.71	0.52 – 0.96	0.02*
Age (≥75 vs. <75 years) within previous PCI (yes)	1.30	0.84 – 1.99	0.23
Previous PCI (yes vs. no) within age (<75 years)	0.84	0.58 – 1.19	0.32
Previous PCI (yes vs. no) within age (≥75 years)	1.53	1.00 – 2.34	0.05*
Age*in-hospital heart failure			
Age (≥75 vs. <75 years) within in-hospital heart failure (no)	0.92	0.71 – 1.20	0.54
Age (≥75 vs. <75 years) within in-hospital heart failure (yes)	0.32	0.12 – 0.85	0.02*
In-hospital heart failure (yes vs. no) within age (<75 years)	0.84	0.39 – 1.82	0.66
In-hospital heart failure (yes vs. no) within age (≥75 years)	0.29	0.14 – 0.57	<0.001**
Age*History of peripheral artery disease			
Age (≥75 vs. <75 years) within history of peripheral artery disease (no)	0.93	0.72 – 1.21	0.60
Age (≥75 vs. <75 years) within history of peripheral artery disease (yes)	0.34	0.14 – 0.80	0.01**
History of peripheral artery disease (yes vs. no) within age (<75 years)	1.28	0.70 – 2.32	0.42
History of peripheral artery disease (yes vs. no) within age (≥75 years)	0.47	0.24 – 0.91	0.02*
Age*Heart rate			
Age (≥75 vs. <75 years) within heart rate (normal)	0.91	0.70 – 1.18	0.47
Age (≥75 vs. <75 years) within heart rate (tachycardia)	0.28	0.09 – 0.85	0.03*
Age (≥75 vs. <75 years) within heart rate (bradycardia)	1.25	0.31 – 5.00	0.75
Heart rate (tachycardia vs. normal) within age (<75 years)	0.67	0.34 – 1.30	0.23
Heart rate (bradycardia vs. normal) within age (<75 years)	0.81	0.33 – 2.01	0.65
Heart rate (tachycardia vs. normal) within age (≥75 years)	0.20	0.08 – 0.52	<0.001**
Heart rate (bradycardia vs. normal) within age (≥75 years)	1.12	0.38 – 3.27	0.84

†All four OR's per interaction term are presented in the table to form an impression of the nature of the interaction. For instance, two separate OR's for former smoker no versus yes for UA and NSTEMI patients and two separate OR's for UA versus NSTEMI for former smoker no and yes. These four OR's are all shown, because when interaction between two factors is added to the model, the OR of one factor may depend upon the level of the other factor. ‡P-value indicates if OR is significantly different from one. *p-value ≤ 0.05; **p-value ≤0.01.Abbreviations: OR, odds ratio; CI 95%, 95% confidence interval; UA, unstable angina; NSTEMI, non-ST-elevation myocardial infarction.

4.4 Discussion

This study aimed to provide insight in the extent of cardiac risk score use in Dutch hospitals as recommended by international cardiac guidelines. In addition, associations with patient-related and hospital-related factors were studied. Substantial variation between hospitals' cardiac risk score use was observed, with in approximately 40% of patient charts a cardiac risk score was not documented. Several patient-related factors including a diagnosis of UA, the presence of in-hospital heart failure, tachycardia and resuscitation at admission were associated with a lower likelihood of cardiac risk score use. Although evidence is not conclusive, the probability of cardiac risk score use was often lower in older patients (≥75 years) with additional conditions, such as in-hospital heart failure, a history of peripheral artery disease or tachycardia.

Previous studies also reported advanced age, heart failure and tachycardia as important predictors of lower guideline adherence in patients with acute coronary syndromes [6,36-41]. Moreover, several of these studies also reported a decreased likelihood of survival [37,38,40]. Implying that patients at high risk for adverse cardiac outcomes are less likely to receive guideline recommended care. However, according to the European guidelines these high-risk subgroups of patients benefit most from early invasive treatments [10]. It may, however, be discussed to what degree an invasive treatment may be desired in these high risk subgroups of patients. Also, it could be questionable to what degree risk stratification using a cardiac risk score adds value in deciding on the treatment for these patients, for example, in the case of resuscitation the decision for a certain procedure may be evident. The European Society of Cardiology guidelines however, do not take these circumstances into account and recommend to estimate risk levels with a cardiac risk scoring instrument for every patient suspected of UA/NSTEMI [10].

Obese patients and former smokers were more likely to have a cardiac risk score documented. The association of former smoking and the use of a cardiac risk score, however, was unexpected and difficult to explain. There are no indications for partial confounding with other factors in the model as ORs for former smoker in univariate and multivariable models are sizeable and similar. Possibly, former smoking is an alias for some other underlying and unknown variable. For instance, former smoking is seen as an indication of a former more high-risk lifestyle and that way affects judgement. Further research may provide more insight on this.

Another interesting finding, that contrasted the findings of previous studies, was that a hospitals' teaching status or the presence of on-site revascularisation facilities were not significantly associated with cardiac risk score use [7,36]. These differences may be explained by the relatively small number of hospitals participating in the present study compared with

previous studies. A large variation between hospitals in adherence scores regarding cardiac risk score use was found. The large component of variance, explained by the random hospital effect, suggests that cardiac risk score use in patients presenting with the same characteristics may heavily depend on which hospital the patient is presented in, and that other factors, beside a hospital's teaching status or on-site revascularisation facilities, are of influence. Common barriers in the implementation of cardiac risk scores, including the absence of necessary resources for implementation and cultural differences, may explain this substantial variation [42]. Also, it has been suggested that physicians find the evidence underlying cardiac risk scores unconvincing [24]. To increase the use of cardiac risk scores in clinical practice several implementation strategies, which pay explicit attention to patients with suspected UA, may be employed. A recent improvement initiative in the USA for instance, in which continuous education was the primary intervention, led to a significant increase in cardiac risk score documentation in patients with UA and NSTEMI [43]. The use of continuous education has proven to be effective in achieving change in practice, however it is recommended to also take into account facilitating factors and barriers on a patient, provider and organisational level [44]. Therefore, further research is needed to carefully understand factors that explain the variation between hospitals' cardiac risk score use.

4.4.1 Study limitations

Several limitations potentially affect the interpretation of the results of this study.

First, the use of cardiac risk scores was measured by screening charts on the documentation of a cardiac risk score. As a result it is unknown to what degree a cardiac risk score influenced physicians' decision making regarding appropriate management strategies. However, it is plausible that when a cardiac risk score was documented, it was also used in practice.

Second, four predictors reported in previous studies of risk score use, that is, aspirin use prior to admission, creatinine level, troponin level and biomarkers, were not considered in the present study. These data could not be abstracted reliably. As a result, the precision of the model reported in this study might be smaller compared with other studies. In addition, it was not possible to reliable extract at what time point a risk score was recorded. The time registered in the patient's file was often imprecise (i.e., time was entered retrospectively and did not represent the actual time point at which the risk score was used) or lacking. Making it impossible to provide any additional contextual information regarding the use of cardiac risk scores in clinical practice.

Third, in two hospitals the method of selection of patient charts differed, as in these hospitals it was not possible to select patients based on the hospital's billing system. This could have influenced the selection of patients. However, their effects may be limited as it appeared that the random effects of these two hospitals were well in range with those of the other hospitals.

Fourth, it was not possible to extract all data from the charts at one time point per hospital. Therefore, monthly data collection visits were deemed necessary. For this reason, the reported associations were corrected for month of discharge. However, the frequent presence of the researchers onsite may have led to more awareness of the healthcare providers using cardiac risk scores, and as a result have higher adherence scores than hospitals not participating in the evaluation of the quality improvement programme. This overestimation of adherence rates can also be a result of the fact that the evaluation of the improvement programme took place in a cohort of highly motivated hospitals, as they all voluntarily agreed to participate.

Finally, three of the randomly selected hospitals declined participation in this study, which may have introduced selection-bias. Hospitals that declined participation were possibly lagging behind in implementation. The actual use of cardiac risk scores in practice might therefore be even lower than estimated in this paper.

4.5 Conclusions

The results of the present study indicate that cardiac risk scores have not been fully implemented in Dutch clinical practice, as a substantial number of patients had no risk score documented in their chart. The large variation between hospitals could not be explained by the presence of on-site revascularisation facilities or a hospitals' teaching status, as well as by several patient-related factors that were associated with higher or lower usage of cardiac risk scores in clinical practice. It is recommended that further research should focus first on explanatory factors for differences between hospitals, which could provide a basis for future improvement initiatives in which strategies are targeted towards patient groups in which risk scores were less often documented, as these patients may currently be undertreated.

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5

Implementation of cardiac risk scores in practice: a qualitative study

Understanding factors that influence the use of risk scoring instruments in the management of patients with unstable angina or non-ST-elevation myocardial infarction in the Netherlands: a qualitative study of health care practitioners' perceptions.

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Abstract

Background

Cardiac risk scores estimate a patient's risk of future cardiac events or death. They are developed to inform treatment decisions of patients diagnosed with unstable angina or non-ST-elevation myocardial infarction. Despite recommending their use in guidelines and evidence of their prognostic value, they seem underused in practice. The purpose of the study was to gain insight in the motivation for implementing cardiac risk scores, and perceptions of health care practitioners towards the use of these instruments in clinical practice.

Methods

This qualitative study involved semi-structured interviews with 31 health care practitioners at 11 hospitals throughout the Netherlands. Participants were approached through purposive sampling to represent a broad range of participant- and hospital characteristics, and included cardiologists, medical residents, medical interns, nurse practitioners and an emergency physician. The Pettigrew and Whipp Framework for strategic change was used as a theoretical basis. Data were initially analysed through open coding to avoid forcing data into categories predetermined by the framework.

Results

Cardiac risk score use was dependent on several factors, including IT support, clinical relevance for daily practice, rotation of staff and workload. Both intrinsic and extrinsic drivers for implementation were identified. Reminders, feedback and IT solutions were strategies used to improve and sustain the use of these instruments. The scores were seen as valuable support systems in improving uniformity in treatment practices, educating interns, conducting research and quantifying a practitioner's own risk assessment. However, health care practitioners varied in their perceptions regarding the influence of cardiac risk scores on treatment decisions.

Conclusions

Health care practitioners disagree on the value of cardiac risk scores for clinical practice. Practitioners driven by intrinsic motivations predominantly experienced benefits in policy-making, education and research. Practitioners who were forced to use cardiac risk scores were less likely to take into account the risk score in their treatment decisions. The results of this study can be used to develop strategies that stimulate or sustain cardiac risk score use in practice, while taking into account barriers that affect cardiac risk score use, and possibly reduce practice variation in the management of unstable angina and non-ST-elevation myocardial infarction patients.

5.1 Background

Cardiovascular diseases, including unstable angina (UA) and non-ST-elevation myocardial infarction (NSTEMI), are among the main causes of death of people across the world [1,2]. International guidelines for the management of UA and NSTEMI [3-5] recommend to treat patients on the basis of their risk for adverse cardiac events such as re-infarction or death. High risk patients can be successfully treated with invasive procedures such as Percutaneous Coronary Intervention (PCI) or Coronary Artery Bypass Grafting (CABG). To accomplish this and to guide physicians in tailored therapeutic decision-making, several cardiac risk stratification scores have been developed [3-5], i.e. the GRACE- [6,7], TIMI- [8], PURSUIT- [9,] FRISC- [10] and HEART [11] scores. Cardiac risk scores comprise of clinical factors associated with adverse cardiac outcomes [12]. The validity of these instruments in terms of their ability to predict the patient's risk of re-infarction or death during hospitalization or after discharge was reported to be good [10,11,13-15]. Previous studies indicate that risk assessment based on physician's experience was inferior compared to risk assessment by using validated risk scores [14,16]. However, despite guideline recommendations and their prognostic value, these instruments are not widely adopted in clinical practice [17]. Practitioner related barriers e.g. knowledge, attitude, behaviour, and external barriers related to the guideline, patient or organization, all affect guideline adherence by physicians [18]. Several studies reported low guideline adherence among physicians when managing UA/NSTEMI patients, resulting in a treatment risk paradox i.e. patients with a low risk of re-infarction or death were more likely to receive invasive treatment strategies (e.g. angiography and/or revascularization) compared to high risk patients [19-26]. Therefore, a gap between evidence-based care and routine clinical practice may exist which could affect patient outcomes negatively [21,27-29]. To improve guideline adherence, quality improvement programs have been initiated in several countries [30-33]. Recently in the Netherlands, such a program was introduced in which, among other things, the use of cardiac risk scores was evaluated [34]. However, to our knowledge, it is unknown to what degree healthcare professionals' perceptions regarding the value of cardiac risk scores in therapeutic decision making may affect the use of these scores in clinical practice. There is also little understanding of factors that facilitate or hinder health care practitioners in their attempts to implement these risk scores in practice. Therefore the objectives of the study are to gain insight in the motivation for implementing cardiac risk scores, and perceptions of health care practitioners towards the use of these instruments in clinical practice.

5.2 Methods

5.2.1 Study design and setting

A qualitative study involving semi-structured interviews was conducted. Professionals employed at cardiology departments of hospitals that previously participated in the evaluation of a Dutch quality improvement program (n=13), were approached for participation in this study. This program aimed to optimize care for patients diagnosed with acute coronary syndromes, including UA and NSTEMI and is based on the recommendations of the European Society of Cardiology guidelines. The hospital sample was verified to be representative for the Dutch population of hospitals, with regard to type of hospital, e.g. teaching versus non-teaching, and the availability of specific cardiac facilities, e.g. PCI or CABG.

5.2.2 Study participants

In each hospital, the cardiologist who was a contact person for the Dutch quality improvement program was approached for participation in the present study. They were selected because they were involved in implementing a cardiac risk score in their institution. After each interview they were asked to recruit or provide contact details of a colleague within their department. They were subsequently approached directly by the researcher (JE) during site visits or by email. Participants were eligible if they were a) currently employed in one of the participating hospitals, b) directly involved in the treatment of UA/NSTEMI patients, i.e. physicians or nurses, c) regardless of their attitude/opinion were experienced in using cardiac risk scores and/or d) involved in the implementation of a cardiac risk score. By means of purposive sampling, the selection of participants ensured diversity on the type of profession, their level of work experience and the type of hospital they worked in.

5.2.3 Development of interview protocol

The interview protocol was structured according to the three dimensions of the Pettigrew and Whipp framework i.e. context, process and content [35] and by reviewing literature about implementation strategies and corresponding barriers and facilitators (Appendix A) [36-39]. For the present study, the three dimensions of the framework were interpreted as following: context; what are motivations behind the use of cardiac risk scores?, process; what strategies are applied to enable, enhance and/or sustain cardiac risk score use and which factors influence this process?, content; what are opinions of health care practitioners towards the value of cardiac risk scores for clinical practice and which effects did they perceive? The interview protocol was pilot-tested with an emergency physician who was involved in the implementation of a cardiac risk score, but was not part of the current research sample. In addition, the adequacy and functionality of the revised interview protocol was discussed within the research team until consensus was reached.

5.2.4 Data collection

Semi-structured interviews were conducted between September 2012 and May 2013. Data were collected on site or at the participant's home. Prior to the interview, participants received an information letter explaining details about the study. All interviews were audio-recorded and transcribed at verbatim unless participants objected. In the latter case, hand written notes were made and a detailed transcription was sent back to the participant for verification (n=1). Interviews were conducted by one member of the research team (JE) who was trained in qualitative interviewing.

5.2.5 Qualitative data analysis

The transcribed interviews were initially analyzed using open coding to avoid forcing data into the predetermined categories i.e. context, content and process. The first five transcribed interviews were coded by two researchers independently, to form an initial code list and to enhance reliability of the analyses process (JE, MJH). Differences between the coding's of the researchers were resolved in consensus meetings. During the analyses of subsequent interviews, the initial code list was further refined by adding new codes or reconstructing existing codes. The definitions of the final code set and the hierarchy of the code structure were reviewed for logic. The final version of the code structure was applied on all transcribed interviews (JE). To ensure concordance in codings, 50% of the transcriptions were coded independently by a second researcher (MJH). Relevant differences in applying the final code structure were discussed and resolved. All transcriptions were reviewed with the revised final code structure by one researcher (JE). To determine if the code structure was sufficient and to ensure no new information occurred (i.e. saturation), three additional interviews were subsequently conducted, transcribed and analyzed40. All data were analyzed in Atlas.ti V.5.7 (ATLAS.ti Scientific Software Development Company, GmbH, Berlin, Germany).

5.2.6 Validation and reliability

Several techniques were used to enable a systematic and transparent process of data collection and analyses. First, after each interview field notes were made which included factual data regarding the interview-setting, observations during the interview, and reflective information regarding thoughts and concerns. They were used to interpret the data more carefully. Second, the interview protocol was consistently used and critically reviewed after each interview. Third, two researchers coded the transcribed interviews independently in ATLAS.ti to manage the coding process. Finally, consensus meetings were held to discuss and reconcile differences in coding of the data. Analytical decisions made in the consensus meetings were documented.

5.2.7 Ethics

Ethics approval was obtained from the medical ethical committee of the VU University Medical Center Amsterdam. Written informed consent for participation and audio-taping of the interview was obtained from all respondents. Confidentiality was assured by removing traceable information from transcripts relating to participating hospitals sited or individuals. Data were stored on a protected network server at the research institute, only accessible to the research team.

5.3 Results

Interviews were conducted at 11 hospitals. Two teaching hospitals with invasive treatment facilities on site refused to participate. One hospital considered interviews too much of a burden for staff, the other hospital did not provide a reason for refusal. In total 37 health care professionals were approached, of which 16 cardiologists, seven medical residents, four medical interns (including one research fellow), three nurse specialists and one emergency physician, were interviewed (Table 5.1). They were familiar with either the GRACE-, TIMI-, FRISC-or HEART risk score at their institution. Six participants could not be interviewed, due to among other a lack of time, resignation or long term absence (Figure 5.1). The average length of an interview was approximately 30 minutes, however, substantial variations in length occurred. The analyses resulted in nine main categories fitted in the dimensions of the Pettigrew and Whipp Framework (Table 5.2). These are elaborated below and illustrated by representing quotations (Appendix B).

5.3.1 Stimuli for implementing cardiac risk scores (context)

Two types of stimuli to implement cardiac risk scores were reported by participants: intrinsic motivations i.e. from within the department and extrinsic motivations i.e. external pressure. In most cases both factors were drivers for cardiology departments to implement a cardiac risk score instrument.

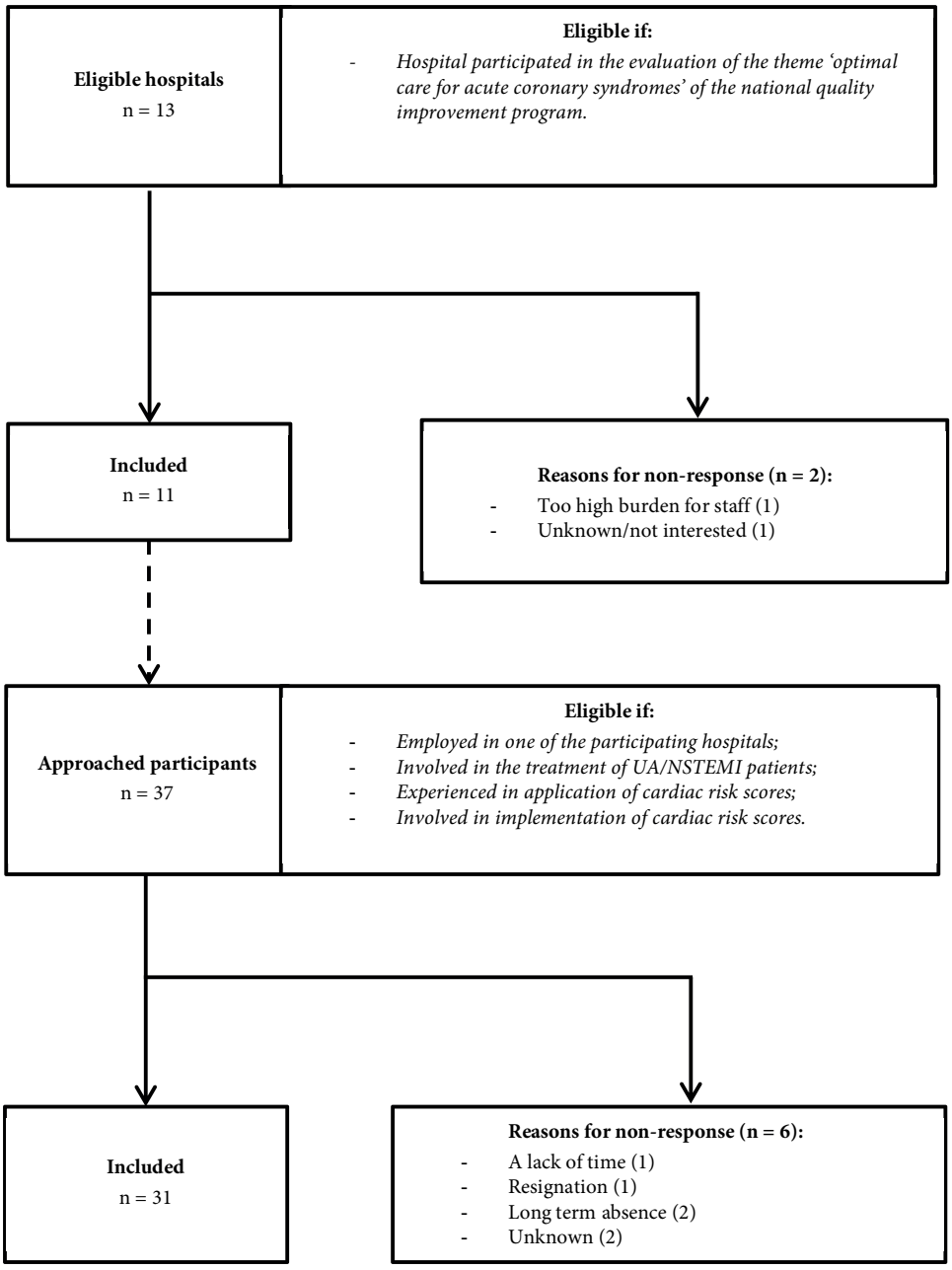

Figure 5.1 Flow diagram of hospital and participant selection

Table 5.1 Hospital and participant characteristics

Hospital characteristics	**No. (%) of hospitals a (n = 11)**
Type of hospital	
Teaching	7 (63.6)
Facilities	
PCI	2 (18.2)
PCI and CABG	3 (27.3)
No revascularization facilities	6 (54.5)
Participant characteristics	**No. (%) of participants a (n = 31)**
Gender	
Male	21 (67.7)
Age (years)	
Mean (SD) / Range	38.9 (9.4) / 26-61
Type and years in profession b	
Cardiologists	16 (51.6)
<5	5 (31.25)
5-10	5 (31.25)
>10	6 (37.5)
Medical resident	7 (22.6)
<5	6 (85.7)
5-10	1 (14.3)
> 10	n.a.
Medical intern	4 (12.9)
< 5	3 (75)
5-10	1 (25)
> 10	n.a.
Nurse specialist	3 (9.7)
< 5	1 (33.3)
5-10	2 (66.7)
> 10	n.a.
Emergency physician	1 (3.2)
<5	n.a.
5-10	1 (100)
> 10	n.a.
Length of interview (minutes)	
Median (IQR)	28.2 (25.6)
< 15	9 (29)
15-30	8 (25.8)
30-45	10 (32.3)
45-60	3 (9.7)
>60	1 (3.2)

Abbreviations: PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; n.a., not applicable. a In no. (%), unless stated otherwise; b Years in current profession/position.

Table 5.2 Themes, categories and concepts

PGF dimensions [a b]	Category	Description	Concepts
WHY context I. Stimuli for implementing cardiac risk scores	Intrinsic motivations	Personal beliefs of health care practitioners that leads to the implementation	• Uniformity problem • Educational support • Research purposes
	Extrinsic motivations	Environmental and organizational pressure that leads to the implementation	• (Inter)national guideline recommendations • Governmental pressure and regulatory demands: quality improvement program, recommendations of Dutch association of cardiology, audits of health care inspectorate • Pressure hospital board • Assessments by health care insurance companies
HOW process II. Process of implementing cardiac risk scores	Implementation strategies	Interventions used to enhance or support the implementation process	• Support and commitment staff • Clinical reminders: posters (passive), written and oral reminders (active) • Data feedback • Education: practical and theoretical • Development project plan • Appointment working committee
	Facilitators and barriers	Influential factors enhancing or hindering the implementation process	*Facilitating factors* • Innovation level: clinical relevance • Practitioner level: commitment staff • Organization level: management support, IT support *Barriers* • Innovation level: administrative burden, complexity of underlying algorithm of risk score, loss of time • Practitioner level: level of work experience, familiarization with new practices, lack of knowledge, lack of relevance • Organization level: frequent staff rotation, high work load, lack of time, lack of management priority, lack of resources, fast update of guidelines, unexpected circumstances

Table 5.2 Themes, categories and concepts *(continued)*

PGF dimensions [a b]	Category	Description	Concepts
HOW process II. Process of implementing cardiac risk scores	Sustainability	Interventions undertaken to sustain change in practices	• Redesigning systems: integration of risk score(s) in existing electronic hospital systems, protocols or clinical pathways • Audit and feedback • Appointment of champions
WHAT content III. Perceptions of health care practitioners	Choice of risk score	Motivation for implementing cardiac risk score and its use in practice	• Choice of risk score based on: purpose, availability relevant parameters, complexity, validity and available scientific evidence, recommendations of clinical guidelines, accordance own practices • Use in practice: type of risk score (GRACE, TIMI, FRISC or HEART), intended users (interns, residents, less often cardiologist, nurse specialists), target group (patients with chest pain, unstable angina, non-ST-elevation myocardial infarction or acute coronary syndrome), location (emergency department, chest pain unit, coronary care unit)
	Unintended benefits and risks	Implementation effects in terms of benefits and risks for quality and safety of care	• Expected benefits: improved uniformity, educational support, scientific benefits • Unintended benefits: support system, enhanced patient safety • Risks: regulatory medicine
	Impact on treatment policies	Impact on physician's decision-making process in terms of admission and treatment policies	• Treatment policy: no consequence, conservative treatments (pharmacological), invasive treatments (cardiac catheterization or revascularization) • Admission policy: admission protocol, patient allocation, patient flow
	Effects on process of care	Effectiveness of cardiac risk score implementation	• Current practice and variation in practice

[a] Pettigrew & Whipp framework. [b] The provided information cuts across more than one dimension.

Intrinsic motivations

The need for a more uniform approach in admission and treatment practices for presenting with suspected UA or NSTEMI was the most commonly mentioned motivation for implementing a cardiac risk score. Also, educational purposes were a frequently mentioned motivation. It was expected that the use of cardiac risk scores created awareness among less experienced physicians in estimating patients' risk of re-infarction or death. Finally, cardiac risk scores were considered of value for scientific research in which they were used to determine the characteristics of the patient population.

Extrinsic motivations

External pressures such as the incorporation of cardiac risk score use in European Society of Cardiology guidelines accelerated the implementation process in several hospitals. In addition, a national quality improvement program stimulated the use of these guidelines and, partly due to its obligatory character, all hospitals aimed to follow these recommendations. Some participants experienced additional pressure from their hospital board to comply with the requirements of the quality improvement program. Other less frequently mentioned pressures were recommendations of the Dutch Association of Cardiology, regulatory audits from the health care inspectorate, and performance assessments by health care insurance companies.

5.3.2 Process of implementing cardiac risk scores (process)

Participants mentioned three complementary categories, which determine the process of implementation: implementation strategies, barriers and facilitators and sustainability.

Implementation strategies

Support of senior staff was considered effective in enhancing the implementation and was accomplished by actively referring to cardiac risk scores e.g. during hand-off sessions. Written reminders to the entire team were applied to pay attention to non-compliance. Also, individuals were personally addressed by one of the senior staff members. Several hospitals used regular data feedback as a strategy to motivate colleagues. To build a consistent knowledge base among medical residents and interns, in all hospitals lectures and personal or written instructions were provided. Finally, other incidentally mentioned interventions, as part of the implementation strategy, were: developing a project plan, establish a working committee and the use of passive reminders, e.g. posters.

Facilitators and barriers

Respondents mentioned that resistance in applying cardiac risk scores was related to the absence of a clinical consequence or critics against the available scientific evidence for using these instruments. Stressing the clinical relevance and importance, especially by the senior

staff, was therefore considered crucial in reducing resistance. Also the administrative burden and complexity of risk score calculations affected its use. In some hospitals this was solved by support from the hospital management board and information technology (IT) department by integrating the calculation and registration of cardiac risk scores in existing software platforms. However, for some risk scores the underlying algorithms were not directly accessible which delayed IT integration.

In explaining low compliance rates, several respondents mentioned that the value of a cardiac risk score in practice was dependent of the professional's experience in cardiology. For example, medical interns were frequently mentioned as benefitting most from using a risk score in founding their treatment decisions in contrast to experienced cardiologists. Moreover, participants noticed that less experienced cardiologists were generally more familiar with clinical prediction models compared to the older. The latter group familiarized themselves more slowly with a cardiac risk scoring instrument. Another barrier in implementing cardiac risk scores was the frequent rotation of medical interns. Continuous education and reminders were necessary to support and sustain the use of cardiac risk scores. Also a high-workload and a lack of available time were frequently mentioned as hindering factors in the application of the risk score. Some cardiologists expressed that external pressures, such as audits, were necessary to be given priority and to receive support of the hospital management board. Other less frequently experienced barriers were a lack of available resources including finances and personnel, lack of relevance (e.g. absence of on-site revascularization options or number of employed cardiology residents), frequent updates of the guidelines and unexpected circumstances including the absence of key persons due to sick leave.

Sustainability

Although most hospitals were in the process of integrating cardiac risk scores in clinical practice, specific strategies were applied to maintain its use on the long term. IT solutions to incorporate cardiac risk scores in the hospital system, including triggers, links and mandatory fields, were helpful reminders. Hospitals without such facilities integrated the cardiac risk score in existing clinical pathways or protocols. Another strategy to maintain cardiac risk score use were periodic audit and feedback sessions. Finally, in some hospitals champions, e.g. a nurse specialist or research fellow, supported by a cardiologist monitored the implementation.

5.3.3 Perceptions of health care practitioners (content)

Perceptions of health care practitioners regarding cardiac risk scores and their use could be allocated in four categories: choice of risk score, unintended and intended benefits and risks, impact on treatment policies, and effects on the process of care.

Choice of risk score

Hospitals aimed to apply cardiac risk scores when patients presented at the emergency department, chest pain unit or the coronary care unit with a suspected or confirmed diagnosis of UA or NSTEMI. Aspects determining the choice for a specific cardiac risk scoring instrument were the purpose of the risk score, availability of the parameters necessary to determine patients' risk, guideline recommendations and scientific evidence. Most hospitals implemented the GRACE risk score. However, applicability of the GRACE was limited due to its dependency on calculators and IT solutions. Some hospitals therefore implemented the TIMI, FRISC or HEART score. Hospitals choosing for the latter preferred a tool that was suitable for a broader category of patients i.e. patients presenting with chest pain to the emergency department.

Unintended and intended benefits and risks

Participants mentioned that implementing a cardiac risk score instrument improved uniformity in treating UA and NSTEMI patients. As a result, participants believed risk scores enhanced patient safety and efficient resource use. Moreover, cardiac risk score use led to a more rapid recognition of high risk patients and created awareness regarding the appropriate site of care. Among interns, cardiac risk scores provided a more clear understanding of the departments' standards regarding the care for UA and NSTEMI patients and increased their awareness of the factors associated with a high risk of adverse cardiac events. Also, its use gave hospitals the opportunity to study illness severity among their population of patients. Participants indicated that the risk score instrument was used as an objective support system to quantify their risk assessment, to confirm their assumptions regarding a patient's risk and/or to justify their chosen treatment plan. Possible risks associated with cardiac risk score use were related to overregulation of the process of care e.g. because participants indicated that mortality risk may be overestimated. Therefore, treatment policies should not be solely based on a risk score.

Impact on treatment policies

Participants reported variation in the degree cardiac risk scores affected the choice between the treatment options. Some participants continued to use conventional risk stratification and clinical experience solely. Others used the risk score as a guide in their decision making, combined with conventional risk stratifiers. In the latter case, cardiac risk scores were mainly used to identify high risk patients who would benefit most from aggressive and timely treatment. In patients with high age, severe heart failure, cognitive impairments and immobility, physicians often deviated from the guidelines as cardiac risk scores could not comprehend the full spectrum of UA or NSTEMI presentations. A few participants mentioned that the risk score also influenced their admission protocol and patient flow. Participants described adjustments in their admission protocols according to the calculated

risk score, for instance low risk patients were either sent home, treated at the outpatient department or admitted to the hospital. Cardiac risk scores were also used to guide patient admission to appropriate sites of care or to enhance the throughput of patients on the emergency department.

Effects on process of care

The implementation of cardiac risk scores resulted in most hospitals in a more uniform approach in supervising interns and in the assignment of (invasive) treatments, though this was disputed by a few participants. They questioned whether hospitals would continue to use cardiac risk scores in daily practice if the national quality improvement program stopped. Actually, a division was observed between hospital departments which implemented a risk score for registration purposes solely, and hospitals in which the guideline recommendations were strictly followed.

5.4 Discussion

This study investigated perceptions of health care professionals concerning the implementation and use of cardiac risk scores in the management of patients diagnosed with UA or NSTEMI.

It appeared that the active involvement of staff members, and the presence of champions responsible for data feedback, sending clinical reminders, education of colleagues and promoting cardiac risk score use on their department were strategies used to implement cardiac risk scores. These were also found in previous studies regarding the evaluation of guideline implementation in cardiology [31,41,42], or guideline dissemination in general [37,43]. In implementing cardiac risk scores, two crucial factors in sustaining their use were mentioned i.e. IT support arranged and prioritized by the hospital board and emphasizing the clinical relevance of the risk score. Apart from the frequent rotation of medical interns, similar barriers in guideline implementation have been reported previously [18,44]. In most hospitals the frequent rotation of medical interns resulted in periodic knowledge deficits which hindered efforts to sustain cardiac risk score use. Previous research regarding underperformance of medical interns or residents identified, among other things, a lack of medical knowledge and poor decision making and clinical judgment skills as underlying problems of underperformance [45,46]. This emphasizes the importance of constant education and feedback in sustaining cardiac risk score use in clinical practice. It is recommended that future quality improvement initiatives take the aforementioned barriers and strategies into account when aiming to improve cardiac risk score use in clinical practice. In addition, future updates of the ESC guidelines could emphasize effective strategies to facilitate cardiac risk score implementation. However, further research is needed to assess the impact of the suggested strategies on risk score adherence.

The results in this study further show that in clinical practice cardiac risk scores were often used as intended, though the impact of the resulting scores on treatment decisions varied and depended highly on the patient's risk of adverse cardiac outcomes. This is in accordance with the European Society of Cardiology guidelines, which recommend to administer therapies tailored to a patient's level of risk [5]. However, it has been reported previously that beliefs about practice and actual practice differ substantially [41]. It is therefore unknown to what degree cardiac risk scores affect clinical decision-making in relation to other information such as electrocardiogram findings or the presence of co-morbidities. This should be studied further. Apart from the risk score's influence on treatment practices, the scoring instruments also functioned as objective support systems in quantifying, confirming and/or justifying physicians' initial risk assessment. Additional benefits, including improved uniformity in treatment practices, educational support and scientific support. These benefits were in concordance with intrinsic motivations of participants prior to risk score implementation. In addition, practitioners who felt forced to use cardiac risk scores were less likely to take into account the cardiac risk score in their treatment decisions or saw a benefit of cardiac risk score use in their own practice, and continued to use conventional risk stratification and base decision making on clinical experience solely. It is therefore recommended for hospital management staff to emphasize and disperse information about these potential benefits of using risk scores throughout their organization.

5.4.1 Study limitations

In interpreting the results of this study, several limitations should be taken into account.
First, to structure the contents of the interviews, the dimensions of the Pettigrew and Whipp framework were slightly deviated from the original framework. This resulted in a thorough analysis of practices in each hospital.

Second, the length of interviews differed considerably between respondents that may have influenced the quality of the data. It appeared that knowledge regarding the implementation of cardiac risk scores differed substantially between participants. Also, some interviews were interrupted because of acute patient admissions. Of these, memo's and transcripts were critically reviewed. Where deemed necessary, follow-up interviews were planned.

Finally, participant checks to enhance external validity were not conducted (except in case the interview was not audio-taped), among other things, because of the likelihood that participants changed their views over time. The information that emerged from the interviews may therefore not be representative for all practitioners involved in the management of patients diagnosed with UA or NSTEMI, and may differ for hospitals not involved in the study. However, we presume these differences to be negligible due to the diversity in participant characteristics and because saturation was obtained. In addition, it

was assumed that audio-taping of the interviews and transcribing verbatim contributed in great extent to the validity of the study results. Also, the use of risk scores is embedded in several international cardiac guidelines. In the Netherlands, it is strongly recommended to use the European Society of Cardiology guidelines in the management of UA and NSTEMI patients. The results of this study could therefore be of use for all practitioners applying these guidelines in the management of UA or NSTEMI patients as the context of care is comparable.

5.5 Conclusions

Health care practitioners disagree on the importance of cardiac risk scores used to decide on the management of unstable angina or non-ST-elevation myocardial infarction patients. Practitioners predominantly experienced benefits in policy-making, education and research when intrinsic motivations were underlying the implementation of cardiac risk scores. In addition, practitioners who felt forced to use cardiac risk scores were less likely to take into account the cardiac risk score in their treatment decisions. The study results can be used to develop effective strategies that stimulate or sustain cardiac risk score use in future practice and reduce practice variation in the management of UA and NSTEMI patients. These strategies may be incorporated in future updates of the ESC guidelines, as currently these do not contain information on how to implement cardiac risk scores in clinical practice. However, several barriers that affect implementation and applicability in practice need to be taken into account.

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Appendix A. Key informant interview guide

Based on the WHY/HOW/WHAT dimensions of the Pettigrew and Whipp framework for strategic change and existing implementation literature (variation in questions asked depended on participants role).

1. **WHY:** What was/were (the) specific motivation(s) for change: why did hospitals wish to implement a cardiac risk score?
   a. At the department level.
   "What was the main incentive to start or continue cardiac risk score implementation in your department?"
   b. In terms of the external context.
   "Has the implementation been guided by factors at the national or organizational level?"
2. **HOW**: What implementation efforts were undertaken to facilitate implementation or to sustain implementation regarding cardiac risk scores?
   a. Effective implementation strategies.
   "Which interventions were applied to implement a cardiac risk score?"
   "Which of these interventions enhanced the implementation process?"
   b. Perceived implementation-related facilitators and barriers.
   "What facilitated implementation activities in your department?"
   "What hindered implementation activities in your department?"
   "What could have been done differently?"
   c. Resource utilization and management support
   "Did you receive management support at the organizational level, if so in what way?"
   "Where necessary resources available for successful implementation?
   "Did intended users receive proper training regarding the use and purpose of cardiac risk score instruments?"
   d. Sustain change.
   "What activities have been taken place to ensure cardiac risk score use over time?"
   "Has the use of cardiac risk scores became part of the risk stratification process at your department?"
3. **WHAT**: What where the perceptions of health care providers regarding cardiac risk scores and what unintended and intended benefits or risks did they experience?
   a. In terms of prior expectations
   "What were expectations prior to implementation and in what extent did they came true?"
   "What is, if so, the additional value of a cardiac risk score to the usual risk stratification process that already existed in your department?"

b. In terms of additional value for risk clinical practice

"What were the effects of introducing cardiac risk scores for your department?"

"What benefits do cardiac risk scores possible bring or brought for your department?"

"What disadvantages do cardiac risk scores possible bring or brought for your department?"

"Has the implementation of a cardiac risk score affected culture or habits in your department? If so, describe the shift?"

c. In terms of application in practice

"What was/were motivation(s) to choose a specific type of cardiac risk score?

"How is the score applied in practice (type of risk score, target group, intended users, location)?

"How do you perceive the user-friendliness of the instrument?"

"Can you describe current practices regarding cardiac risk score use?"

Source: Pettigrew AM, Whipp R. Managing Change for Competitive Success. Oxford: Blackwell Publishing; 1993.

Appendix B. Representative quotations

PGF dimension	Category	Representative quotes
I. Stimuli for implementing cardiac risk scores (context)	Intrinsic motivations	In practice we ran into an uniformity problem regarding admission decisions and choice of drug therapy. We wanted to translate the structure that you have in your head as a physician, when making a risk assessment, to a score (…). This is often a feeling, while a score is a way to structure this, to justify (…). In the past it was not clear where choices were based on (…). This led to uncertainty and a lack of clarity among the medical interns working at the emergency department (Cardiologist, teaching hospital, PCI facilities). …in particular to explain to interns, that this is a risk stratification model, which can be used to determine the risk of mortality and that it may have implications for your treatment. More as a tool for education I think, than that we often based (treatment) decisions on it in the past (cardiologist, teaching hospital, PCI facilities). Actually, it started as just registering risk factors for scientific purposes, not so much for practice purposes. We started with the TIMI early 2000 (…) with the idea to use it for research and to compare patient groups (cardiologist, teaching hospital, PCI facilities).
	Extrinsic motivations	The latest guidelines, of last year, indicate that you should perform risk stratification. It is up to yourself to determine how you accomplish that. A risk score is most convenient. (…) It is possible that the quality improvement program was an extra stimuli. However, complying with the guidelines is part of your job, so… (cardiologist, teaching hospital). It is, in particular, introduced because of the fact that it is an indicator of the quality improvement program. I honestly think that otherwise, in most clinics in the Netherlands, it would be without obligations. And that is no more (cardiologist, teaching hospital, PCI facilities). First, these sort of things (i.e. quality indicators) are requested from authorities e.g. health care insurances and health care inspectorate. Second the standardization of treatment, an unambiguous policy. Even among us (i.e. cardiology staff) (cardiologists, general hospital). The manager intensive care has told the cardiologists: 'these are the requirements of the quality improvement program, where you have to start working on' (emergency physician, general hospital).
II. Process of implementing cardiac risk scores (process)	Implementation strategies	So, what was my role in it? I have presented the guidelines and the GRACE score to the staff, held a few presentations about it, discussed all the guidelines and then we decided (with fellow cardiologists) to implement the new guidelines in practice. (..) First you have to agree as a team that you are going to use it. Second, that you have to explain what the GRACE is, where it comes from and what the reason behind the implementation is (cardiologist, teaching hospital).

PGF dimension	Category	Representative quotes
II. Process of implementing cardiac risk scores (process)	Facilitators and barriers	That you really need it to make a treatment decision. I can imagine, if that is not the case, that at one point the (…) score will no longer be used. That there will be a re-lapse on conventional risk factors (cardiologist, teaching hospital). (…) once again you must link it to a policy change. So you have to say in case of a low score we do this and in case of a high score we do that. As long as you don't do that, it has no point, except for registration. (…) It should be an incentive to implement something in which you can improve care. As long as you only implement it to register: waste of time (research fellow, teaching hospital, PCI facilities). That you really need it to make a treatment decision. I can imagine, if that is not the case, that at one point the (…) score will no longer be used. That there will be a re-lapse on conventional risk factors (cardiologist, teaching hospital). That you really need it to make a treatment decision. I can imagine, if that is not the case, that at one point the (…) score will no longer be used. That there will be a re-lapse on conventional risk factors (cardiologist, teaching hospital). (…) once again you must link it to a policy change. So you have to say in case of a low score we do this and in case of a high score we do that. As long as you don't do that, it has no point, except for registration. (…) It should be an incentive to implement something in which you can improve care. As long as you only implement it to register: waste of time (research fellow, teaching hospital, PCI facilities). (…) Look, some of the data should be automatically extracted with that electronic file of ours. So, basically, blood pressure, heart rate, age and renal function, can all be extracted without you having to think about it. And then, you make it (a) mandatory and (b) easy. Then you can do so much more with it (cardiologist, teaching hospital). If the bosses (staff) don't ask for it, then it's gone within two weeks. So, it must be useful for the patient, that is motivation number one. And if it is really useful, everybody will continue using it by himself of course. If it is a bit more questionable, you need someone to sit behind you rags and immediately point it out to you. Especially if it is the boss himself. If that is absent as well, than such a registration is doomed. Nothing will happen anymore (research fellow, teaching hospital, PCI facilities). There is a fast rotation of interns, which hinders the introduction and sustainability of an instrument. I continuously have to point out the use of the instruments, until this leads to saturation. Once the acquaintance is there, a new group of interns arrives. This makes it difficult. Also, there is a lack of knowledge among the interns: a lot of newcomers in a short period of time (cardiologists, teaching hospital, PCI facilities).

PGF dimension	Category	Representative quotes
II. Process of implementing cardiac risk scores (process)	Facilitators and barriers	High workload. And I must say that the interns fill it out very well. Maybe it is more a point of attention for the cardiologists. But I have no evidence for that (nurse specialist, general hospital). (…) There are people who really feel summoned to apply the HEART score, and others think 'for me this is not necessary'…..or 'I will do this at the nursing ward'. They don't understand the sooner you sustain a trajectory, it is just finished. That's what I notice. Young cardiologists are educated with safety management systems and criteria you have to pay attention to. More conservative specialists, who have been working here for a long time, but that counts for all specialism's, say: 'we do that for years, why should we adjust that?' (emergency physician, general hospital).
	Sustainability	And I do have the idea that everybody tries to fill them in as best as possible. But look, it (risk score) is not integrated in the [name electronic patient file], which of course would be fantastic. If you admit someone with an acute coronary syndrome and then get such a standard fill out table. Then, I think, it will always be done well (medical intern, teaching hospital). Namely nurse specialists are very suitable for that, they are good in reasoning from protocol and in mapping of these trajectories. They are trained to implement that both in the nursing echelon as in the medical. And in that manner nurse specialists are a valuable addition for our clinical operations (cardiologists, general hospital).
III. Perceptions of health care providers (content)	Choice of risk score	That one (i.e. GRACE) is more extensively validated, more accurate, more well-known, plus it is recommended as first choice by the guidelines. It is more useful for the clinic, than the FRISC score I think. But he is slightly more complicated. (research fellow, teaching hospital, PCI facilities) The considerations for risk stratification is, at this moment, that the TIMI score is a more simpler tool and especially because there is too little support from the IT department to support the GRACE. That actually means that it is more convenient for your normal workflow to choose the TIMI score. While we actually have seen that the GRACE score is more often used and also should be, within our guidelines, the recommended risk score (…) (cardiologist, general hospital).
	Choice of risk score	Well… it is (HEART score) well applicable in the group of patients that we get presented on the emergency department. While the GRACE and in particular the TIMI are much more focused on a selected group of patients who….yeah, a bit disrespectful put, you already know that you have to act acutely on. While it is, especially with the group of interns we have here, important to correctly select the right group of patients arriving at our emergency department (cardiologist, general hospital).

PGF dimension	Category	Representative quotes
III. Perceptions of health care providers (content)	Unintended and intended benefits and risks	It's just easy, I find, in the work process if you can apply scores. If you work with young people, let me put it in this way, then protocols, guidelines and scores are easy for decision making. And I work here with young people (emergency physician, general hospital). In their thinking- and learning process that pink form (i.e. risk score) works extremely well. Because, we ordered to fill it out, but what does it mean? They have to immerse oneself in it. They receive some explanation, but after that they have to apply it themselves. So for interns it is a very good learning tool (nurse specialist, general hospital). Yes, well another benefit is when you start doing research. Database research at yourself (i.e. in your own patient population). Then it provides you with extra information regarding the type of patients you have. You could stratify them on the basis of a risk score. And you could say, well, this category patients functions like this, and this category functions like that, and this so (cardiologist, teaching hospital, PCI facilities). Well, because every treatment brings morbidity and mortality. Every pill, every PCI, you name it. Everything gives morbidity and mortality. And that only balances out, if the normal prognosis has a higher morbidity and mortality. Than you are allowed to administer that certain treatment. Otherwise you damage everybody with that treatment. Well, if you know this, and you have a risk model for it, than you should really use it. Because otherwise it means that, if you would give everybody the maximum treatment, you would over-treat two thirds of people who you damage (…) (cardiologist, teaching hospital, PCI facilities). Yes, I think that a disadvantage can be that you overestimate people in terms of mortality risk and that you might, unnecessarily, earlier catheterize them or treat them invasively. And that you incorrectly consider people as unstable angina pectoris, while the diagnosis was different, but due to the high GRACE score you choose that (i.e. invasive) path, while otherwise you might have thought harder about an alternative diagnoses. However, it is difficult to say if that actually is the case, it might (medical resident, teaching hospital).
	Impact on treatment policies	Fast administration of medication, fast and clear policies. That enhances the patient flow on the emergency department, and that is of course where I do it for. Because my emergency department is for fast diagnostics and rapid treatment, but also for quickly deciding on the correct location of care: to an intervention center, or upstairs (e.g. coronary care unit of cardiology ward), or home. That is, what I want to have clear as soon as possible. And not that people are waiting here for hours (emergency physician, general hospital).

PGF dimension	Category	Representative quotes
III. Perceptions of health care providers (content)	Impact on treatment policies	Yes, exactly. It is decisive for the antiplatelet therapy. And in addition we use the GRACE score for the moment of catheterization. So if someone has a high GRACE score, than he will be considered earlier for catheterization (medical resident, teaching hospital, PCI facilities). Ehm, no. The standard policy is that you work conform the guidelines. The GRACE actually adds not much to it (cardiologist, general hospital).
	Effects on process of care	There are people who don't take it into account, who have no feeling with it at all, who think it is nonsense… (cardiologist, teaching hospital, PCI facilities) It will also have to do with individuals. That one person has more belief in it, and that others experience it as a burden: something has to be done again. That people find it sometimes difficult, like they are not taking good care of their patients. While I think that's not the case. Only it is not verifiable without such a scoring system. Anyway, that differs per individual. I think when a person has little feeling with scoring systems or numbers, they are less willing to adopt it and register it. I think it depends in great extent on that. If you look at the differences, the periods of scoring here in the hospital, you see that it very much fluctuates. And to me it seems that it has partly to do with that (cardiologist, general hospital).

6

Clinical decision-making of cardiologists: design of a clinical vignette study

Clinical decision-making of cardiologists regarding admission and treatment of patients with suspected unstable angina or non-ST-elevation myocardial infarction.

This chapter has been adapted from: Engel J, Van der Wulp I, Poldervaart JM, Reitsma JB, De Bruijne MC, Wagner C. Clinical decision-making of cardiologists regarding admission and treatment of patients with suspected unstable angina or non-ST-elevation myocardial infarction: protocol of a clinical vignette study. BMJ Open 2015;5:e006441.

Abstract

Background

Cardiologists face the difficult task of rapidly distinguishing cardiac related chest pain from other conditions, and to thoroughly consider whether invasive diagnostic procedures or treatments are indicated. The use of cardiac risk scoring instruments has been recommended in international cardiac guidelines. However, it is unknown to what degree cardiac risk scores and other clinical information influence cardiologists' decision making. This paper describes the development of a binary choice experiment using realistic descriptions of clinical cases. The study aims to determine the importance cardiologists put on different types of clinical information, including cardiac risk scores, when deciding on the management of patients suspected of unstable angina or non-ST-elevation myocardial infarction.

Methods and analysis

Cardiologists are asked, in a nationwide survey, to weigh different clinical factors in decision making regarding patient admission and treatment using realistic descriptions of patients in which specific characteristics are varied in a systematic way (e.g. web based clinical vignettes). These vignettes represent patients suspected of unstable angina or non-ST-elevation myocardial infarction. Associations between several clinical characteristics, with cardiologists' management decisions will be analysed using generalized linear mixed models.

Ethics and dissemination

The study has received ethics approval and informed consent will be obtained from all participating cardiologists. The results of the study will provide insight into the relative importance of cardiac risk scores and other clinical information in cardiac decision making. Further, the results indicate cardiologists' adherence to the European Society of Cardiology guideline recommendations. In addition, the detailed description of the method of vignette development applied in this study could assist other researchers or clinicians in creating future choice experiments.

6.1 Background

About six percent of the emergency department presentations are due to chest pain [1]. Of these patients, a substantial number are diagnosed with an acute coronary syndrome, including unstable angina (UA), non-ST segment elevation myocardial infarction (NSTEMI) and ST segment myocardial infarction (STEMI) [1,2]. Mortality after an acute coronary syndrome is substantial [3,4]. To prevent cardiac damage or mortality, timely treatment is indicated. As a result, the attending physician has the difficult task to rapidly distinguish cardiac related chest pain from chest pain caused by other conditions. Patients presenting with chest pain to the emergency department should therefore be stratified according to their level of risk of having a cardiac condition [5]. Risk assessment is generally based on a patient's clinical history, physical examination, biomarkers and electrocardiogram findings [6-9]. The decision for hospital admission or type of treatment is dependent on a patients' risk of adverse cardiac events, such as re-infarction or mortality. The European Society of Cardiology guidelines on the management of UA or NSTEMI recommend to treat patients at high risk of re-infarction or death with invasive procedures or treatment (e.g. coronary angiography, Percutaneous Coronary Intervention (PCI) or Coronary Artery Bypass Grafting (CABG)) [7]. To determine the patient's risk, several cardiac risk scores have been developed and validated i.e. the HEART [5], GRACE- [10,11], TIMI- [12], FRISC- [13] and PURSUIT score [14]. Use of these instruments is recommended by professional guidelines [7]. Despite the availability of valid cardiac risk stratification tools and recommendations of their use, in previous studies, low risk patients were more likely to receive invasive procedures compared to high risk patients [15-18]. Such a treatment risk paradox implies low adherence rates with the guidelines, which possibly affects or even threatens patient safety on the one hand and results in suboptimal resource use on the other hand. Low guideline adherence might be explained by barriers affecting physicians' attitude towards guideline recommendations [19], including disagreement with the guidelines or unwillingness to adopt the guidelines. In addition, previous research indicates that physicians may consider evidence underlying the guidelines as unconvincing [20]. As a result, they may depend heavily on their own personal experience and seem to underestimate important risk factors [21,22]. In this study we focus on cardiologists' decision making in the management of UA and NSTEMI. To our knowledge it is unknown to what degree cardiac risk scores and other clinical information influence their decisions about admission and choice of treatment. The objective of the present study is twofold. First, to determine the influence of a cardiac risk score upon cardiologists' decision on patient admission and treatment. Second, to determine the relative importance of different types of clinical information, in the presence or absence of a risk score, upon management decisions concerning suspected UA or NSTEMI patients.

6.2 Methods

6.2.1 Study design

To determine how cardiologists weigh different clinical factors (e.g. relative importance) in their decision to admit or to treat a patient, binary choice experiments are conducted using vignettes of clinical cases. Two decision moments were investigated, the decision to admit a patient to hospital and the decision to perform cardiac catheterization. In the vignettes the clinical factors are systematically varied according to a fractional factorial design.

6.2.2 Study population

Cardiologists working as a registered cardiologist in a Dutch hospital will be approached for participation in this study by email. They will be recruited through the Dutch directory of physicians.

6.2.3 Data collection

The data will be collected using a web-based survey, presenting cardiologists with clinical vignettes. The clinical vignettes describe patients by means of a set of attributes, reflecting characteristics of a patient or treatment [23]. Clinical vignettes are a frequently applied approach to study decision-making in health care as they closely reflect clinical practice [24]. In addition, clinical vignettes were shown to be a valid tool to measure the quality of care [25,26]. Cardiologists will be asked to complete a web-based survey containing the clinical vignettes. Prior to completing the survey, cardiologists will be informed about the global study objective and asked to give consent for participation in the study. Cardiologists who initially fail to respond will be sent reminders one, three, eight and twelve weeks after first sending the survey. The completion time of the survey will be approximately 20 minutes and cardiologists are able to stop and continue completion of the survey at any time. The data will be processed anonymously.

Survey

The survey registers demographic characteristics, including year of birth, gender, current profession, years of cardiology care experience, whether cardiologists are still actively involved in the care for patients diagnosed with UA or NSTEMI and which risk score they apply in clinical practice. In addition, associated hospital characteristics such as type of hospital they work in and whether hospitals have revascularization facilities on site will be registered. After completing the section that registers demographic characteristics, cardiologists are presented with the vignettes. These are presented in two parts that differ in the decision that needs to be made. In the first part of the survey (A), the clinical vignettes describe patients who present themselves with chest pain to the emergency department. Cardiologists are asked to indicate on a binary scale (yes or no) whether he or she would discharge the patient from

the emergency department without any further diagnostic testing (e.g. no serial troponin testing or exercise testing). In addition, cardiologists are asked on a three point Likert scale how certain they are of their decision (very sure, sure, somewhat sure). The clinical vignettes in the second part of the study (B) describe a patient's condition when the patient is already admitted to the hospital with a high suspicion of UA or NSTEMI. Cardiologists are asked to indicate whether he or she would advise an invasive procedure i.e. coronary angiography within 72 hours from admission and how certain they are of their decision (using the same three point Likert scale). Cardiologists are asked to make decisions that reflect their actual clinical practice as closely as possible. The survey was pretested among two cardiology residents, not involved in the design of the study, and asked to provide feedback regarding the applicability of the survey. This provided insight in the comprehensiveness of the survey, and the time it takes to complete the survey.

Pre-selection of attributes

Potential attributes relevant for the management of UA and NSTEMI, regarding the decision to admit or treat a patient, were selected from clinical guidelines. It was assumed that these guidelines provided an integral overview of the published scientific evidence and therefore cover all relevant attributes [6-9]. Further, variables of validated risk scoring instruments [5,10-14], the website 'up-to-date' [27-29], and recently conducted interviews on the use of risk stratification instruments in practice [30], were reviewed for additional relevant attributes. The website 'up-to-date' concerns an evidence-based resource that aims to support physicians in clinical decision making.

Initially, all aspects that can be taken into account when stratifying risk were selected from the aforementioned sources, which resulted in a pre-selection of 105 potential attributes. As Dutch cardiologists are most familiar with the European Society of Cardiology guidelines in treating their patients, the pre-selection was subsequently reduced by selecting only those attributes that were mentioned in this guideline and in the validated risk scoring instruments. This left 56 attributes that were considered of importance for the present study (Table 6.1).

Final selection of attributes and attribute levels

As it is cognitively difficult for respondents to take into account large numbers of attributes, it is recommended – although there is no standard – to select between six to ten attributes in choice experiments [31-33]. This approach was followed in the present study. The final set of attributes was selected by a panel of three cardiologists in collaboration with the research team during a consensus meeting (1st of October 2013). These cardiologists were selected based on their affinity with research, and were chosen to reflect diversity in experience and type of hospital they work in. In preparing the consensus meeting, the cardiologists were asked to write down in order of importance the six to eight most important attributes

when deciding to discharge a patient presenting with acute chest pain from the emergency department without further diagnostic testing (decision moment A). Equally, they listed attributes that were important in deciding on performing a coronary angiography within 72 hours in patients with a high suspicion of UA or NSTEMI (decision moment B). In case a cardiologist indicated that an attribute is essential in decision making, he had the option to select an additional attribute, on top of the six to eight that were already selected. The attributes selected by the cardiologists were the starting-point for the consensus meeting.

The selected attributes were compared and discussed. Furthermore, the cardiologists reviewed and compared the pre-selection of potential attributes derived from the European Society of Cardiology guidelines and existing risk scoring instruments. After viewing this list, the cardiologists were given the opportunity to change their own attribute selection into a final selection. None of the cardiologists made any changes in their selection. Again, differences and similarities were discussed until consensus was reached over a final set of eight attributes for decision moment A and seven attributes for decision moment B (Table 6.2 and 6.3).

The arguments whether to select or remove a specific attribute were written down in a logbook. After determining the final set of attributes, the selection and description of attribute levels was discussed and confirmed / approved. In selecting attribute levels, we aimed to select levels that closely reflect the variety of presentations in clinical practice and will be easily understood by cardiologists. A secondary goal in selecting attribute levels was to keep the total number of possible vignettes i.e. the full factorial design, as small as possible. Therefore the number of levels within an attribute were kept to a minimum. The expert panel was re-approached by email to provide a further review of the selected attributes and attribute levels per decision moment on the basis of their initial feedback.

Cardiac risk score

In developing the clinical vignettes, initially cardiac risk score was considered as an attribute. However, this led to unrealistic vignettes and the attribute was therefore removed from the full factorial design. Additionally, by using the HEART risk score[5] (for decision moment A) and GRACE 2.0 risk score [34] (for decision moment B), cardiac risk was estimated for every vignette. This was accomplished by entering the values present in the vignette while holding the remaining parameters constant.

The sample of cardiologists will, prior to completion of the survey, be divided in two groups. One group will complete vignettes without a cardiac risk score being present, while the other group completes the vignettes with a cardiac risk score present. Cardiologists will be instructed to consider the risk score as the one familiar from their own practice or knowledge.

Table 6.1 Pre-selection of attributes (after removal of duplicates)

Category	Attribute	Source†
Demographics	1 Older age >75 years	ESC, RS
	2 Gender	ESC, RS
Risk factors	3 Presence of risk factors in general (e.g. positive family history, peripheral artery disease, carotid stenosis, diabetes mellitus, kidney failure, smoking, hypertension, hypercholesterolemia, obesity)	ESC, RS
	4 Diabetes mellitus	ESC, RS
	5 Chronic kidney failure/ creatine level	ESC, RS
	6 Heart failure	ESC, RS
	7 Depressed left ventricular ejection fraction	ESC
	8 Killip-class classification	ESC, RS
	9 Anemia	ESC
	10 Obesity	ESC, RS
	11 Malnutrition	ESC
History	12 Known coronary artery disease	ESC, RS
	13 Previous myocardial infarction	ESC, RS
	14 Previous or recent percutaneous coronary intervention	ESC
	15 Previous or recent coronary artery bypass surgery	ESC
	16 Severity of coronary artery disease	ESC
	17 Cocaine use	ESC
	18 Aspirin use 7 days prior to admission	RS
Clinical presentation	19 Anamnesis suspicious for cardiac related chest pain	RS
	20 Persistent angina pectoris	ESC, RS
	21 Symptoms of angina pectoris in rest	ESC
	22 Reoccurring angina pectoris	ESC
	23 Several episodes of angina pectoris after event	ESC
	24 Tachycardia	ESC, RS
	25 Hypotensive	ESC, RS
	26 Hemodynamically instable	ESC
	27 Increased leucocytes at presentation	ESC
	28 Thrombocytopenia at presentation	ESC
	29 Increased bleeding risk	ESC
	30 Presence of bleeding	ESC
	31 Intermediate or high GRACE risk score	ESC
	32 Positive stress test	ESC
	33 Cardiac arrest at admission	ESC, RS
Electrocardiogram findings	34 ECG ST segment changes	ESC, RS
	35 ECG deviations at rest	ESC
	36 Dynamic ST/T changes	ESC
	37 Negative T waves	ESC
	38 ST depression	ESC
	39 ST elevation	ESC
	40 Ventricular arrhythmia	ESC

Table 6.1 Pre-selection of attributes (after removal of duplicates) (continued)

Category	Attribute	Source†
Laboratory results	41 Elevated troponin levels	ESC
	42 Elevated biomarkers	ESC, RS
	43 Hyperglycemia	ESC
	44 Elevated C-reactive protein	ESC
	45 Elevated B-type natriuretic peptide	ESC
Context information	46 Re-vascularization status	ESC
	47 Rest ischemia	ESC
	48 Severity of lesions	ESC
	49 Physical condition of patient	ESC
	50 Fragility of patient	ESC
	51 Cognitive decline	ESC
	52 Functional decline	ESC
	53 Physical dependence	ESC
	54 Quality of life	ESC
	55 Patient's wishes	ESC
	56 Risks versus benefits of re-vascularization	ESC

† Attributes are derived from the European Society of Cardiology guideline 2011 and from the GRACE-, TIMI-, FRISC-, PURSUIT- and/or HEART risk score. Abbreviations: ESC, European Society of Cardiology guideline; ECG, electrocardiogram; GRACE, Global Registry of Acute Coronary Events; RS, risk score.

Selection of clinical vignettes

The attributes and levels for decision moment A comprised $2^3 3^5 = 1944$ possible combinations in the full factorial design, where the base of the formula concerns the number of levels of an attribute and the exponent concerns the number of attributes with respectively two or three levels. For decision moment B, $2^3 3^4 = 648$ possible vignette combinations could be created. It is practically impossible to present respondents with such a vast amount of vignettes, therefore a fractional factorial design was created to reduce the number of vignettes for each decision moment. In selecting vignettes, the aim was to estimate the main effects of all attributes. The quality of the selection of vignettes was compared to a theoretical optimum by means of the G efficiency parameter which ranges between 0 (inefficient design) and 1 (efficient design). The G efficiency parameter is a useful guide when judging fractional factorial designs [35]. For both decision moments (i.e. discharge without further testing and prompt coronary angiography), the number of vignettes were reduced to 64. The vignettes selection showed substantial G efficiency of 0.94 for decision moment A and 0.95 for decision moment B. Per decision moment, the 64 scenarios were randomly allocated into eight blocks containing eight scenarios each. This is to ensure that all attribute levels will appear with equal frequency in each block [36]. Prior to sending the survey, cardiologists will be randomly assigned a block

Table 6.2 Final selection of attributes and attribute levels of decision moment A

Clinical setting: Patient presenting with acute chest pain at the emergency department.
Decision: 'Would you send this patient home without any further diagnostic testing (e.g. no serial troponin testing or exercise testing)?'

Attribute	Attribute level
Age	< 50 years
	years
	> 75 years
Gender	Male
	Female
Known coronary artery disease	No
	Yes
Chest pain classification based on history taking	A-specific chest pain
	Atypical angina pectoris
	Typical angina pectoris
Symptoms of chest pain still present at presentation	No
	Yes
Risk factors†	No risk factors
	One risk factor
	More than one risk factor
ECG	Normal
	Atypical changes
	Typical ischemic changes
Troponin‡	Below reference level and representative
	Below reference level, not representative
	Above reference level

number in SPSS and being sent the corresponding questionnaire. Each survey comprises 16 scenarios in total (8 per decision moment).

Case description of clinical vignettes

Two members of the research team drafted the initial clinical case descriptions of the vignettes: one representing decision moment A and one representing decision moment B. Next, the clinical case descriptions were discussed and reviewed in a second consensus meeting (26 February 2014), comprising four cardiologists and the research team. This review process was undertaken to ensure accuracy, plausibility and clarity of the clinical event presentation in all of the vignettes. The vignettes were revised until both the research team as the panel of cardiologists agreed that the case descriptions represented clinical practice as closely as possible. An example of a vignette is presented in Box 6.1.

Table 6.3 Final selection of attributes and attribute levels of decision moment B

Attribute	Attribute level
Age	< 70 years
	70-80 years
	80 years
Renal function	No renal dysfunction
	Mild to moderate renal dysfunction
	Severe renal dysfunction
Known coronary artery disease	No
	Yes
Persistent chest pain	No
	Yes
Risk factors†	No risk factors
	One risk factor
	More than one risk factor
ECG	Normal
	Atypical changes
	Typical ischemic changes
Troponin‡	Normal at repeated measures
	Significant rise and/or 'rise and fall'

6.2.4 Study outcome

The study outcome is the relative importance cardiologists' put on different types of clinical information, both in the presence and absence of the risk score, when deciding on the management of suspected UA or NSTEMI patients.

6.2.5 Statistical considerations

Demographic characteristics will be presented using descriptive statistics. Associations of independent variables with the binary responses of cardiologists on the clinical vignettes in the survey will be studied with a generalized linear mixed model (GLMM), taking into account random effects for blocks and cardiologists. In total, four models will be created i.e. two for each decision moment taking into account the presence or absence of cardiac risk score information. In the analyses, cardiologists' responses (yes or no) are the binary outcome measure. Independent variables are the attributes, risk score (if present in the vignette) and the degree of certainty of respondents' answers. All independent variables will be simultaneously included in the analyses. A significance level of $p \leq 0.05$ will be used. The analysis with the GLMM will be performed by Laplacian integration, conducted in R for windows (V.3.0.2) with package lme4 [37]. The impact of the presence of the risk score on a cardiologist's decision will be studied by comparing results of the analyses with and without presenting risk score information in the vignettes.

Box 6.1 Example of clinical vignettes used in the web-based survey

Decision moment I (with risk score)
You see a 65 year or old woman with aspecific complaints of chest pain at the emergency department. At presentation the complaints are absent. The patient is known with coronary artery disease, but has no other risk factors [a]. The ECG is normal and the troponin at arrival is below the reference level and representative [b]. You calculate a risk score [c], which gives an intermediate risk.

1. Would you send this patient home without any further diagnostic testing (e.g. exercise testing)?
   - yes
   - no

2. How sure are you of your answer?
   - very sure
   - sure
   - somewhat sure

Decision moment II (with risk score)
You see a 65 year old patient, suspected of instable coronary artery disease (UA/NSTEMI), who stays in hospital for observation. Since presentation, the patient has persistent symptoms of chest pain. The patient has no history of coronary artery disease (CAD), but has more than one classical risk factors[a]. The ECG is normal and troponin levels are at repetition normal[b]. Further, the lab results show no presence of renal failure. You calculate a risk score [c], which gives a low risk .

1. Would you perform coronary angiography within 72 hours in this patient?
   - yes
   - no

2. How sure are you of your answer?
   - very sure
   - sure
   - somewhat sure

[a] risk factors: diabetes mellitus, hypertension, hypercholesterolemia, smoking and positive family history
[b] according to your hospital's standards
[c] calculated risk according to risk score applied in your own practice (for instance, GRACE, TIMI, FRISC, PURSUIT or HEART score.

6.2.6 Sample size

In total, each cardiologist will complete 16 vignettes (8 for decision moment A and 8 for decision moment B). In calculating the minimum number of cardiologists needed, the following formula is followed: n=500(c /(at)). In this formula, 'n' is the minimum number of cardiologists, 'c' is the largest number of levels for any of the attributes, 'a' is the number of alternative scenario's that cardiologists are presented with and 't' is the total number of choice scenarios per decision moment that each cardiologist is presented with [38,39]. In this study a minimum sample size of, 500(3/(18)), approximately 188 cardiologists are needed per group (with or without a cardiac risk score) to study main effects for decision moment A and B separately. The Dutch directory of physicians contains 963 cardiologists. If a response of 40% is assumed, 385 cardiologists will complete 16 vignettes in total, which will be sufficient for estimating main effects.

6.2.7 Ethics and dissemination

The study protocol was reviewed and approved by the medical ethical committee of the VU University Medical Center Amsterdam (protocol number: 2014008). A waiver of active informed consent was granted, as the study concerns completely anonymized data. A form of informed consent, however, will be conducted at the start of the survey when cardiologists are asked to consent that their answers will be used and stored for scientific purposes. Results are planned to be disseminated in two papers submitted to peer reviewed journals, and presentations at relevant conferences.

6.3 Discussion

UA and NSTEMI are two conditions that are associated with high mortality rates. Correctly estimating patients' risk of re-infarction or death and taking into account this risk in selecting a management strategy is of importance in preventing unnecessary deaths and optimal use of resources. Cardiac guidelines recommend the use of several sources of information to estimate the risk for an individual patient. However, it is unknown to what degree cardiologists take into account all these aspects in the management of patients suspected of UA or NSTEMI. As mentioned in the introduction several studies report a treatment risk paradox, i.e. low risk patients were more likely to receive invasive procedures compared to high risk patients. Implying that cardiac risk scores are not used or not of importance in decision making regarding admission or invasive treatment. The results of the present study will provide further insight in the complex decision regarding admission and treatment of UA and NSTEMI patients, and concern the degree of adherence to the European Society of Cardiology guideline recommendations. The results of this study could therefore be of interest for all practitioners applying these guidelines in the management

of UA or NSTEMI patients. And are needed to reduce the variation in practice between cardiologists, hospitals and countries, and as a result find an optimal balance between correctly identifying UA or NSTEMI patients from the large pool of chest pain patients presenting at the emergency department who would benefit most from invasive treatment on the one hand and unnecessary admissions or resource use on the other. Also, this study provides other researchers or clinicians aiming to set up a clinical vignette study with a thorough methodological description of all research steps.

6.3.1 Potential limitations

In developing the study, several methodological limitations occurred which potentially affect interpretation of the findings. First, in this study the outcome measure concerns a complex decision to be made within a limited period of time in a sometimes hectic environment. The vignettes in this study are limited to respectively seven and eight attributes for each decision moment while in clinical practice cardiologists may take into account other aspects in their decision making, for instance bleeding risk scores in deciding on coronary angiography. Also cardiologists are not able to see the patient at hand which may influence decision making. However, clinical vignettes have proven to be a valid and valuable tool to measure the quality of care in previous studies [25,26].

Second, the pre-selection of attributes involved in UA/NSTEMI management was minimized to the European Society of Cardiology guidelines and to variables from existing risk scoring instruments, as it is cognitively impossible to take into account all attributes. Some attributes are therefore neglected. However, as Dutch cardiologists are most familiar with the European Society of Cardiology guidelines it was considered reasonable to derive attributes from these guidelines.

Finally, the calculated sample size was based on an assumption that every cardiologists reviews the same number of vignettes. In the present study however, every cardiologist reviews the same number of vignettes, but not all cardiologists will review the same vignettes due to the blocked design. The effect of ignoring this assumption may be limited as it is previous suggested that a minimum number of six assessments per scenario is sufficient [40]. With the present sample size calculation, this requirement is met.

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Selecting patients with NST-ACS for coronary angiography: a nationwide clinical vignette study in the Netherlands

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Abstract

Background

Cardiac guidelines recommend that the decision to perform coronary angiography (CA) in patients with Non-ST-Elevation Acute Coronary Syndrome (NST-ACS) is based on multiple factors. It is, however, unknown how cardiologists weigh these factors in their decision-making. The aim was to investigate the relative importance of different clinical characteristics, including information derived from risk scores, in decision-making of Dutch cardiologists regarding performing CA in patients suspected for NST-ACS.

Methods

Web-based survey, containing clinical vignettes. Registered Dutch cardiologists were approached to complete the survey, in which they were asked to indicate whether they would perform CA for 8 vignettes describing 7 clinical factors: age, renal function, known coronary artery disease, persistent chest pain, presence of risk factors, electrocardiogram findings and troponin levels. Cardiologists were divided into two groups: group 1 received vignettes without a risk score present, while group 2 completed vignettes with a risk score present.

Results

129 (of 946) cardiologists responded. In both groups, elevated troponin levels and typical ischemic changes ($P<0.001$) made cardiologists decide more often to perform CA. In contrast, severe renal dysfunction ($P<0.001$) made cardiologists more hesitant to decide on CA. Age and risk score could not be assessed independently, as these factors were strongly associated. Inspecting the factors together showed e.g. that cardiologists were more hesitant to perform CA in elderly patients with high risk scores than in younger patients with intermediate risk scores.

Conclusions

When deciding to perform in-hospital CA (≤ 72 hours after patients admission) in patients suspected of NST-ACS, cardiologists tend to rely mostly on troponin levels, ECG changes and renal function. Future research should focus on why CA is less often recommended in patients with severe renal dysfunction, and in elderly patients with high risk scores. In addition, the impact of age and risk score on decision-making should be further investigated.

7.1 Background

The management of patients with Non-ST-Elevation Acute Coronary Syndrome (NST-ACS), including Non-ST-Elevation Myocardial Infarction (NSTEMI) and Unstable Angina (UA), is challenging. Physicians deal with the difficult task of identifying patients at high risk for adverse cardiac events who would benefit most from invasive therapies, such as percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), while preventing unnecessary invasive procedures in low risk patients in whom conservative therapies are appropriate [1]. Recent guidelines from the European Society of Cardiology (ESC) for the management of patients with NST-ACS recommend that cardiologists base their decision regarding coronary angiography (CA) and subsequent treatments on multiple factors, including a patients' cardiac history, risk factors for coronary artery disease, results from physical examination, laboratory results and electrocardiogram (ECG) findings [1,2]. Furthermore, it is recommended that physicians use objective risk scoring instruments, such as GRACE or TIMI, in guiding risk stratification and management [1-5]. In patients at intermediate or high risk for cardiac adverse events, CA within respectively 72 or 24 hours after hospital admission is indicated, except in case of severe contra-indications such as active bleeding or the presence of major comorbidities [1,2]. Timing of CA and, if indicated, subsequent revascularization should thus be based on the patient's risk status. Previous studies, however, demonstrated that patients at high risk for cardiac adverse events were often less likely to undergo CA than low risk patients [6-11]. A possible explanation for such a treatment risk paradox may be cardiologist's reluctance to perform invasive procedures in patients with high risk features, such as high age and acute heart failure, because of a perceived increased risk of procedure-related adverse events (i.e. contrast-induced kidney injury, bleeding, stroke, or even death) [1,2,12-14]. Further, a recent study in thirteen Dutch hospitals showed that compliance to cardiac risk scores in clinical practice is relatively low and that risk score use varies largely between hospitals [15]. However, data were collected retrospectively, and it is therefore unknown whether the information derived by using a cardiac risk score actually influenced cardiologists treatment decisions in this recent study. The exact importance of various clinical characteristics and risk score outcomes on the decision to perform prompt invasive management remains unclear. Therefore, the aim of this study was to investigate the relative importance of different clinical characteristics, including information derived from risk scores, in the decision-making of Dutch cardiologists regarding performing CA in patients suspected for NST-ACS.

7.2 Methods

This study used a binary choice experiment to study the relative importance of different clinical characteristics, including information derived from risk scores, in the decision-making of Dutch cardiologists.

7.2.1 Survey

A web-based survey containing the binary choice experiments was sent to all 946 cardiologists who were registered in the Dutch directory of physicians in the year 2014. The survey started with an informed consent procedure, explaining the purpose of the study and the option to decline participation. To describe respondents' characteristics, each cardiologist was subsequently asked to register his/her age, gender and working experience in years. In addition, they were asked whether they are employed in a hospital with a teaching status (yes/no), with revascularization options (no, PCI, or PCI/CABG) and whether they used a cardiac risk score at the coronary care unit. Responding cardiologists who were retired or no longer active in practice were excluded from analysis. For a detailed description of the study, we refer to the previously published study protocol [16].

7.2.2 Factors: selection and choice of levels

The binary choice experiments consisted of vignettes of clinical cases. Based on literature review and expert opinion seven essential factors representing clinical characteristics were identified on which cardiologists were likely to base their decision to perform CA, that is: age, renal function, known coronary artery disease, persistent chest pain, presence of risk factors for coronary artery disease (i.e. diabetes mellitus, hypertension, hypercholesterolaemia, smoking and a positive family history), electrocardiogram findings and high sensitive troponin levels. Respondents were instructed to interpret the factor troponin levels (positive/negative) according to their own hospital standards. The factors have different levels, which are depicted in Table 7.1. In addition to the aforementioned factors, the patient's cardiac risk of adverse events was estimated for every clinical vignette by using the GRACE 2.0 risk score leading to the following risk categories: low, intermediate, and high [17]. This was accomplished by entering the values present in the vignette, and entering similar values of 'severity' for the remaining parameters (i.e. diuretic use, heart rate, systolic blood pressure, Killip class and cardiac arrest at admission) in every vignette.

The sample of cardiologists was divided into two groups before the start of the survey [16]. One group completed the vignettes without a cardiac risk score being present (group 1), while the other group completed the vignettes with a cardiac risk score present (group 2). Cardiologists in the latter group were instructed that the reported risk categories were generated by the risk score that they apply in their own practice, as it was not specified that it was the result of the GRACE 2.0 risk score.

7.2.3 Experimental design

The vignettes were systematically varied on the aforementioned clinical factors (factorial design): age, renal function, known coronary artery disease, persistent chest pain, presence of risk factors, electrocardiogram findings and troponin levels. When combining all factors and factor levels, $2^3 3^4$=648 unique clinical vignettes were created (full factorial design). From these vignettes, a G-optimal design of 64 vignettes was selected that allowed for estimation of all main effects, employing the computer algorithm implemented by Wheeler [18]. The 64 scenarios were randomly allocated to eight blocks containing eight vignettes each. Cardiologists were randomly assigned to a block of eight vignettes. For each of the eight vignettes included in the survey, cardiologists were asked to decide whether they would perform CA within 72 hours after patient admission or would not perform CA (yes or no).

Table 7.1 Final selection of factors and their levels

Clinical setting: patient with suspected NST-ACS is admitted for observation in the hospital.
Decision: 'would you perform coronary angiography within 72 hours in this patient?'

Factors	Factor levels		
Age	< 70 years	70-80 years	>80 years
	65 in clinical vignette	75 in clinical vignette	85 in clinical vignette
Renal function	No renal dysfunction	Mild to moderate renal dysfunction	Severe renal dysfunction
Known coronary artery disease	No		Yes
Persistent chest pain	No		Yes
Risk factors†	No risk factors	One risk factor	>One risk factor
ECG	Normal	Atypical changes	Typical ischemic changes
Troponin‡	Normal at repeated measures		Significant rise and/or 'rise and fall'

† diabetes mellitus, hypertension, hypercholesterolemia, smoking and a positive family history; ‡ According to cardiologists' own hospital standards

7.2.4 Data analysis

The strength of associations between independent variables (i.e. factors) and decisions of cardiologists in the survey (yes/no CA) were estimated using a generalized linear mixed model (GLMM) for binary response data, and expressed as odds ratios (ORs). Random effects for cardiologists were added to this model to account for the clustering of data within cardiologists. Separate GLMM models were created for group 1 (vignettes without a risk score) and group 2 (vignettes with a risk score). The various factors, the variable risk score (group 2 only) and the block factor were simultaneously entered as fixed effects to the model. Since the number of blocks is relatively small, blocks were not introduced as random effects in the model as the associated component of variance cannot be estimated with acceptable accuracy. For that reason block effects were introduced as fixed effects in the analysis. As a check for partial confounding / near multicollinearity, in Table 7.4, ORs from multivariable analyses (and their standard errors and confidence intervals) were compared with ORs from univariable analyses (at all times including fixed block effects and random cardiologists effects in the model). Significance tests were based on the likelihood ratio test. In addition, for independent factors with three factor levels, pairwise comparisons, i.e. level 1 vs. 2, level 1 vs. 3, and level 2 vs. 3, were made using the Wald test. Effect sizes were expressed in terms of ORs and their associated 95% CI. p-values equal to or below 0.05 were considered significant. The impact of the presence of the risk score on a cardiologist's decision was studied by comparing ORs and p-values of the analyses of group 1 with group 2. The analyses with the GLMM were conducted in R for windows (V.3.1.3) [19].

The multivariable GLMMs of the two groups were used to determine the relative importance of each factor in deciding on CA. Relative importance refers to the contribution of a specific factor to the total deviance (-2log likelihood) of the multivariable model. It was calculated by taking the difference between the deviances of the multivariable model with all factors present and a model with one of the factors of interest removed. The resulting differences were converted to percentages for each factor by dividing the difference by the sum of contributions of all independent factors, multiplying by 100 [20]. Interpretation of relative importance measures is similar to the percentage of variance accounted for in ordinary regression.

In the study protocol, we considered the degree of perceived certainty of decisions as a possible covariate in the GLMM [16]. Effectively, this implies that results are 'corrected' for uncertainty. However, since uncertainty is an integral part of the decision process, analyses that 'corrected' for uncertainty led to results that could not be properly interpreted and the variable was not included in the analyses.

7.3 Results

7.3.1 Study population

A total of 946 Dutch cardiologists, 470 in group 1 and 476 in group 2, were approached by email to complete the survey. A total of seven reminders were sent between June and October 2014. Eventually, 14% (66/470) and 13% (63/476) of the cardiologists responded. In each group, the answers of nine participants were not eligible for analysis, due to either missing informed consent, incomplete data or because cardiologists were not active in practice anymore (Figure 7.1). The final sample consisted of 57 cardiologists in group 1 and 54 cardiologists in group 2. The majority of cardiologists who completed the survey were male, had more than 10 years of clinical experience, and were employed in a hospital with both PCI and CABG options. There were no significant differences in characteristics of the cardiologists between group 1 and group 2 (Table 7.2). Detailed information regarding responses of cardiologists on the clinical vignettes is provided as supplementary material (Appendix A).

7.3.2 Relative importance of clinical factors

Group 1: vignettes without risk score present

For group 1, the following factors affected cardiologists' decisions to perform CA within 72 hours the strongest (in decreasing order): troponin levels (48.9%), ECG changes (17.9%), renal function (11.8%), age (9.5%), persistent chest pain (6.4%), previous CAD (2.9%) and presence of risk factors (0.5%) (Table 7.3). When changing from one level of a factor to another, the probability for deciding to perform CA may be relatively strongly affected, i.e. for troponin levels, or modestly affected, i.e. for presence of risk factors. This is what is reflected in the percentage for relative importance of a factor and in the estimated odds ratios.

Of the two factors affecting cardiologists' decisions the strongest, patients with a significant rise and/or 'rise and fall' of troponin levels, or with typical ischemic changes on the ECG, were more likely to receive CA compared to patients with normal troponin levels or with no changes or atypical changes on the ECG. Severe renal dysfunction compared to no renal dysfunction or mild to moderate renal dysfunction, and older age (>80 years) compared to younger patients (<70 and 70-80 years) made cardiologists decide less often to perform CA. Presence of persistent complaints of chest pain or a history of CAD hardly seemed to affect cardiologists' decisions. The presence of risk factors was not significantly ($p=0.43$) associated with the decision whether or not to perform CA. The strengths of the multivariable associations are presented in terms of ORs and associated 95% CIs. Also, in parentheses the ORs and CIs of the univariable analyses are presented for comparison (Table 7.4).

Group 2: vignettes with risk score present

For group 2, the following factors impacted cardiologists' decisions to perform CA within 72 hours the strongest (in decreasing order): troponin levels (49.6%), renal function (14.9%), risk score (14.3%), ECG changes (9.8%), persistent chest pain (6.7%), presence of risk factors (0.7%), age (0.6%), and previous CAD (0.00%).

Cardiologists decided more often to perform CA in patients with a significant rise and/or 'rise and fall' of troponin levels than in patients with normal troponin levels. In patients with severe renal dysfunction, cardiologists were less likely to perform CA compared to patients with no or mild to moderate renal dysfunction. For patients with typical ischemic changes on the ECG cardiologists decided more often to perform CA than for patients with no changes or for patients with aspecific ECG changes. Cardiologists were also more likely to perform CA for patients with persistent complaints of chest pain than for patients without such complaints. Presence of risk factors, age, and previous CAD were not significantly associated with the decision to perform CA, with p-values ranging between 0.45 – 0.75. The strengths of the multivariable associations are presented in terms of ORs and associated 95% CIs. Also in parentheses the ORs and CIs of the univariable analyses are presented for comparison (Table 7.4).

Information derived from a cardiac risk score was in the top three factors that influenced cardiologists' decisions the most. Although the likelihood ratio test suggested a significant effect of the availability of a risk score on the decision to perform CA (p=0.02), subsequent pairwise comparisons between the three levels of risk score with the Wald test did not provide conclusive evidence about the nature of this effect. Associated p-values of the Wald test were all above 0.05. Further analyses revealed that there was a strong association (i.e. partial confounding) between the provision of a risk score and a patient's age as presented in the vignette. Conclusions about the contributions of age and risk score by inspecting these factors separately could therefore not be made. The combined factor for age and risk score, however, was significantly associated with the decision to perform CA (p=0.003). This despite problems with convergence of the multivariable model, possibly related to fairly extreme probabilities connected to age lower than 70 years and low-risk score, and age higher than 80 years and high-risk score. In elderly patients (>80 years) with high-risk scores, cardiologists were more hesitant in their decision to perform CA than in younger patients with intermediate risk scores; OR of 0.15 (95% CI 0.05 – 0.46) for 70-80 years versus age older than 80 and OR of 0.13 (95% CI 0.04 – 0.83) for the comparison of patients younger than 70 and older than 80 years. Further, in younger patients (<70 years) with low risk scores, cardiologists were more likely to decide on performing CA than in patients with intermediate risk scores aged between 70 and 80 years (OR = 4.58, 95% CI 1.88 – 11.14).

Table 7.2 Demographics of participating cardiologists

	Group 1† (n=57)	Group 2‡ (n=54)	P-value∞
Gender			0.803
Male	48 (84.2%)	44 (81.5%)	
Age≈	50.0 (42.0-59.0)	49.5 (41.0-55.0)	0.125
< 50 years	26 (45.6%)	27 (50.0%)	
≥ 50 years	31 (54.4%)	27 (50.0%)	
Working years≈	12.0 (7.0-24.0)	11.0 (5.0-21.0)	0.172
< 5 years	7 (12.3%)	11 (20.4%)	
5-10 years	18 (31.6%)	16 (29.6%)	
> 10 years	32 (56.1%)	27 (50.0%)	
Revascularization options			0.805
No	18 (31.6%)	15 (27.8%)	
Yes, PCI	13 (22.8%)	11 (20.4%)	
Yes, PCI and CABG	26 (45.6%)	28 (51.9%)	
Teaching hospital			0.424
Yes	35 (61.4%)	38 (70.4%)	
Use of risk score at CCU*			0.177
Yes	41 (71.9%)	45 (83.3%)	

≈Median and accompanied 25th and 75th percentile. All other data are presented in n(%). Abbreviations: PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; CCU, coronary care unit. † Group 1 refers to the group of responding cardiologists receiving the set of vignettes without a risk score present. ‡ Group 2 refers to the group of responding cardiologists receiving the set of vignettes with a risk score present. ∞ Goodness of fit test, for continuous variables with the Mann-Whitney U test, and for categorical variables with Pearson's chi-square test or Fisher's Exact Test. *Being GRACE, TIMI, FRISC, and HEART risk score.

Block effects

Although block effects are significant ($p \leq 0.05$), the percentage explained deviance for blocks was relatively small: 2.1% in group 1 and 3.4% in group 2). For group 2, the analysis without blocks in the model yielded similar results, except for factor risk score: the percentage explained deviance for risk score dropped from 14.3% to 3.8%. Again, we have to concede that conclusions with respect to the impact of risk score alone on performing CA cannot be drawn with sufficient confidence.

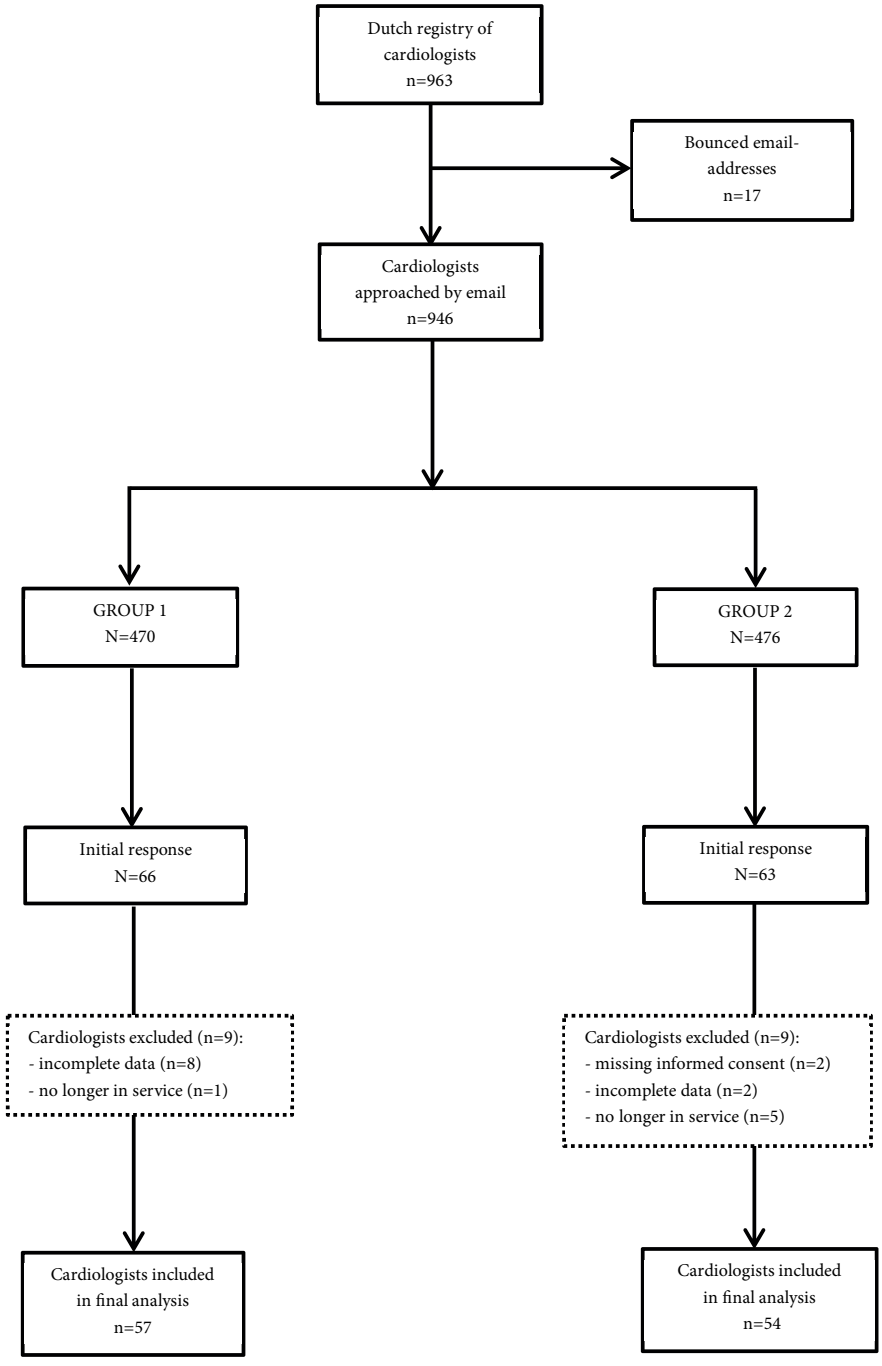

Figure 7.1 Flow chart of respondent selection and survey response.

Table 7.3 Importance of each factor in deciding whether or not to perform coronary angiography

Group 1				Group 2			
Order of importance	**Factor**	**Explained deviance%†**	**P-value‡**	**Order of importance**	**Factor**	**Explained deviance%†**	**P-value‡**
1.	Troponin	48.9%	≤0.001	1.	Troponin	49.6%	≤0.001
2.	ECG	17.9%	≤0.001	2.	Renal function	14.9%	≤0.001
3.	Renal function	11.8%	≤0.001	3.	Risk score outcome	14.3%∞	0.02
4.	Age	9.5%	≤0.001	4.	ECG	9.8%	≤0.001
5.	Persistent chest pain	6.4%	≤0.001	5.	Persistent chest pain	6.7%	≤0.001
6.	Previous CAD	2.9%	≤0.001	6.	Risk factors	0.7%	0.45
7.	Risk factors	0.5%	0.43	7.	Age	0.6%∞	0.50
8.	Risk score outcome	n.a.	n.a.	8.	Previous CAD	0.0%	0.75
	(blocks)Δ	(2.1%)	--		(blocks) Δ	(3.4%)	--
	Total	100%			Total	100%	

†loglikelihood from a single attribute divided by the sum of partial loglikelihoods of all factors ‡P-value based on the loglikelihood test. ∞Factor risk score outcome is partially confounded with factor age, and therefore its impact cannot be interpreted. Δ explained deviance due to the allocation of cardiologists to blocks in the experimental design. Abbreviations: CAD, coronary artery disease; ECG, electrocardiogram; n.a., not applicable.

Table 7.4 Univariable and multivariable associations between a positive decision to order a CA and factors using Generalized Linear Mixed Models (GLMM)

	GROUP 1 (n=57 cardiologists) *Univariable analysis*			**Multivariable analysis**			**GROUP 2 (n=54 cardiologists)** Univariable analysis			**Multivariable analysis**		
Factor	*Raw % CA = yes∞*	*OR*	*95% CI LL-UL*	*OR*	*95%CI LL–UL*	*P-value†*	*Raw % CA = yes∞*	*OR*	*95% CI LL-UL*	*OR*	*95%CI LL–UL*	*P-value†*
Troponin levels												
Elevated	80.6	13.7	8.25 – 22.69	66.90	26.29 – 170.25	≤0.001	84.9	11.57	7.14 – 18.76	55.80	22.50 – 138.36	≤0.001
Normal	26.9	1.0		1.0			33.9	1.0		1.0		
ECG changes‡						≤0.001						≤0.001
Aspecific	43.0	1.04	0.66 – 1.65	1.13	0.54 – 2.39	0.74	49.3	1.13	0.71 – 1.82	2.00	0.88 – 4.56	0.10
Typical ischemic	74.7	4.17	2.51 – 6.92	15.39	6.37 – 37.17	≤0.001	77.7	4.05	2.41 – 6.79	16.40	4.80 – 56.05	≤0.001
Normal	42.8	1.0		1.0			46.4	1.0		1.0		
Age‡						≤0.001						0.50
70-80 years	65.0	1.81	1.13 – 2.89	1.21	0.58 – 2.49	0.61	72.8	2.58	1.56 – 4.26	1.08	0.28 – 4.18	0.91
>80 years	42.0	0.72	0.45 – 1.14	0.14	0.05 – 0.34	≤0.001	49.7	0.97	0.60 – 1.55	0.58	0.10 – 3.48	0.55
<70 years	51.7	1.0		1.0			51.4	1.0		1.0		
Presence of risk factors‡						0.43						0.45
1 risk factor	51.0	1.01	0.64 – 1.61	0.82	0.35 – 1.91	0.65	59.3	1.07	0.66 – 1.74	0.69	0.30 – 1.59	0.38
> 1 risk factor	58.2	1.40	0.88 – 2.22	1.32	0.61 – 2.85	0.48	59.0	1.08	0.68 – 1.72	1.09	0.50 – 2.39	0.83
No risk factors	49.7	1.0		1.0			56.0	1.0		1.0		
Renal dysfunction‡						≤0.001						≤0.001
Mild to moderate	54.1	0.62	0.38 – 0.99	0.52	0.23 – 1.18	0.12	64.3	1.36	0.84 – 2.21	2.17	0.84 – 5.60	0.11
Severe	39.4	0.33	0.21 – 0.54	0.09	0.04 – 0.21	≤0.001	51.4	0.76	0.47 – 1.21	0.25	0.10 – 0.63	≤0.001
No	66.0	1.0		1.0			58.7	1.0		1.0		
Previous CAD												
Yes	61.4	2.08	1.42 – 3.04	2.80	1.45 – 5.42	≤0.01	57.3	0.93	0.63 – 1.37	0.94	0.50 – 1.78	0.75
No	44.1	1.0		1.0			59.0	1.0		1.0		
Persistent chest pain												
Yes	63.2	2.29	1.57 – 3.36	4.90	2.36 – 10.16	0.000	68.4	2.36	1.56 – 3.51	3.79	1.92 – 7.51	0.000
No	43.6	1.0		1.0			48.2	1.0		1.0		

Table 7.4 Univariable and multivariable associations between a positive decision to order a CA and factors using Generalized Linear Mixed Models (GLMM) (continued)

Risk score outcome‡						n.a.					0.02
Intermediate	n.a.	n.a.	n.a.	n.a.	n.a.	63.7	4.41	2.60 – 7.49	4.40	0.84 – 22.93	0.08
High	n.a.	n.a.	n.a.	n.a.	n.a.	71.8	6.32	3.21 – 12.42	1.27	0.09 – 18.20	0.86
Low	n.a.	n.a.	n.a.	n.a.	n.a.	32.7	1.0		1.0		

Abbreviations: CAD, coronary artery disease; ECG, electrocardiogram; LL, lower limit; LRT, loglikelihood ratio test; n.a., not applicable; OR, odds ratio; 95% CI, 95 percent confidence interval; UL, upper limit.
†Significance tests for independent factors were based on the loglikelihood ratio test (in bold).
‡Significance tests for independent factors with three levels pairwise comparisons, i.e. level 1 vs. 2, level 1 vs. 3, and level 2 vs. 3, were based on the Wald test (in italic).
∞ Raw percentages of patients receiving CA for each level of a factor are presented. E.g. in group 1, for factor Troponin, 222 vignettes are in category 'elevated' and 179 of these received CA, leading to 179 / 222 x 100 = 80.6 %.
Associations comparing level 2 versus 3 for the different factors were:
- ECG changes: typical ischemic versus aspecific (GROUP 1: P 0.000, OR 13.57, CI 95% 5.65 – 32.60) / (GROUP 2: P 0.000, OR 8.20, CI 95% 2.87 – 23.46)
- Age: >80 years versus 70-80years (GROUP 1: P 0.000, OR 0.11, CI 95% 0.05 – 0.27) / (GROUP 2: P 0.25, OR 0.53, CI 95% 0.18 – 1.55)
- Presence of risk factors: > 1 risk factor versus 1 risk factor (GROUP 1: P 0.21, OR 1.61, CI 95% 0.77 – 3.36) / (GROUP 2: P 0.22, OR 1.56, CI 95% 0.76 – 3.32)
- Renal dysfunction: sever versus mild to moderate (GROUP 1: P 0.000, OR 0.17, CI 95% 0.07 – 0.39) / (GROUP 2: P 0.000, OR 0.12, CI 95% 0.05 – 0.26)
- Risk score outcome: high versus intermediate (GROUP 2: P 0.14, OR 0.29, CI 95% 0.06 – 1.50)

7.4 Discussion

When deciding to perform in-hospital CA (within 72 hours after patients admission) in patients suspected of NST-ACS, cardiologists tend to rely mostly on the following three sources of clinical information: troponin levels, ECG changes and renal function. In our binary choice experiment, cardiologists decided more often to perform CA in vignettes representing patients with elevated troponin levels and in patients with typical ischemic changes on the ECG. In contrast, in vignettes representing patients with severe renal dysfunction, cardiologists seemed to be more hesitant to perform CA. Persistent complaints of chest pain, previous coronary artery disease and the presence of risk factors had limited impact on the decision whether or not to perform CA. Since effects of risk score were strongly associated (i.e. partial confounding) with age, no firm conclusions could be drawn about the separate contribution of risk score and age on cardiologists' decisions.

With CA, there is a small risk for complications. It is therefore recommended by the guidelines that physicians take several criteria into account when assessing a patient and subsequently deciding on a conservative or invasive approach [1,2,21,22]. In the current study, troponin and ECG changes were considered most important in decision-making, which is in line with the guideline recommendations where both factors are defined as primary features of high risk for adverse cardiac events, and thus with a clear indication for invasive management [1,2]. The guidelines consider patients with (severe) renal dysfunction as high risk for adverse cardiac events as well, and therefore recommend invasive treatment. However, the results in our study suggest that cardiologists were less likely to opt for CA in patients with severe renal dysfunction compared to patients with mild to moderate or no renal dysfunction. This treatment risk paradox, in which patients at low risk for adverse cardiac events are more likely to receive invasive treatment than high-risk patients, has been reported on before in NST-ACS patients with renal dysfunction [23-25].

Although several studies demonstrated that invasive treatment in patients with severe renal dysfunction was associated with a reduction in rehospitalisation together with a significant reduction or trends of reduced risk for death and re-infarction [12,26-28], cardiologists seem to be hesitant to perform CA. A possible explanation may be that cardiologist are hesitant to perform CA, as severe renal dysfunction is associated with an increased risk of complications [1,22]. Another explanation could relate to the available scientific evidence regarding the benefits of early invasive therapy in NST-ACS patients with renal dysfunction. For instance, in an editorial on this topic, the author points out that there is conflicting evidence regarding the benefits of early invasive management in this patient group, and that the majority of studies have observational study designs (instead of experimental designs), which can encompass an increased risk of confounding, and/or have relatively small study samples [29].

Just as in patients with severe renal dysfunction, a treatment risk paradox was present in elderly patients at high risk for adverse cardiac events based on a cardiac risk score outcome. Cardiologists seemed to be more hesitant to opt for CA in patients over 80 years with a high-risk score than in patients at intermediate risk and of a younger age. As mentioned before, perceived increased risk for complications of treatment and less benefit for the older patient and patients with renal dysfunction probably plays a role here. Future research should focus on why in these specific patient groups the guidelines are not adhered too.

It has been suggested before that cardiologists may not take all predictors of adverse cardiac events into account when deciding on CA [9,30,31]. This was also the case in our study, where information regarding a patient's cardiac history and presence of risk factors hardly influenced cardiologists decision-making. Cardiac risk scores incorporate all important clinical factors, and therefore could be, when actively used in practice, a solution to the aforementioned treatment-risk paradox. In the past decade, several prospective studies demonstrated that risk scores were superior to clinical assessment by the physician alone [31-33]. This emphasizes the importance of multi-factorial risk assessment as recommended by the guidelines. Further prospective research regarding the impact of these scores on decision-making and patient outcomes is necessary, given that in this study we were not able to determine the exact impact of risk score on decision-making.

7.4.1 Study limitations

Several limitations should be taken into account. First, although cardiologists were repeatedly contacted, the response rate was low. In the study protocol it was described to achieve a response rate of 40%, resulting in 385 cardiologists, to estimate main effects. This sample rate is, however, not reached. Nevertheless, despite the wider confidence intervals of odds ratios, several significant associations were found. Therefore, this study provides further insight into decision processes of cardiologists offering a valuable contribution to the modest number of studies conducted in the field of decision-making in cardiology so far.

Second, possibly only cardiologists with an affinity for scientific research participated (i.e. selection bias). The study sample consisted mainly of cardiologists who were male, 50 years or older and with more than 10 years of experience in clinical practice. However, this pattern was the same for both groups of cardiologists, and thus comparable in demographics. Unfortunately statistics regarding the average age and years in practice of all cardiologists in the Netherlands were not available, making an assessment of the generalizability of the study results difficult.

Third, despite our study design, it remained difficult to determine individual contributions of age and risk score as these factors were strongly associated (i.e. hampered by confounding).

Fourth, the decisions made on the basis of vignettes can be different from decisions made in a real-life situation in clinical practice where the patient can actually be observed at the coronary care unit. In addition, daily practice other factors – not included in this vignette study – might influence cardiologists' decisions. However, results were generally consistent with findings from earlier studies. Further, clinical vignette studies have shown to be the most practical, cost-effective and at the same time thorough and valid approach to measure the process of decision-making [34,35].

Finally, the time frame in which cardiologists were asked to decide on CA was set on 'performing CA within 72 hours after patient admission (in-hospital)'. Given the recommendations in the latest guidelines [2], in which it is not so much a question if CA should be performed but rather when, it can be debated that timing of CA is also of interest to investigate. For instance, by adding more variation in response categories, e.g. immediately, within 24 hours, or within 72 hours. However, it was not the aim to measure whether the 'correct' decision was made, but to gain insight into which factors influence decisions the most. Furthermore, the latest guidelines were published after data collection was finished, and it can be argued that the 2011 guidelines are still up to date, as implementation of guidelines in practice takes a considerable amount of time.

7.5 Conclusions

When deciding to perform in-hospital CA (within 72 hours after patients admission) in patients suspected of NST-ACS, cardiologists tend to rely mostly on the following three sources of clinical information: troponin levels, ECG changes and renal function. The importance of age and risk score in separation was difficult to assess, due to strong association between these factors. However, in elderly patients at high risk of adverse cardiac events according to a risk score, cardiologists seemed to be more hesitant to perform CA than in younger patients with intermediate risk scores. Just as in patients with severe renal dysfunction. Future research should focus on decision-making regarding CA in these patient groups, and on the impact of age and risk scores on decision-making.

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Appendix A. Summary of cardiologists' response in terms of number and percentages of vignettes

Factors	Vignette Response, N (%) Group 1 *Cardiologists n=57* *Vignettes n=456≈*		Group 2 *Cardiologists n=54* *Vignettes n=432≈*	
	CA yes *242(53.1%)*	**CA no** *214(46.9%)*	**CA yes** *251(58.1%)*	CA no *181(41.9%)*
Troponin†				
Significant rise and/or 'rise and fall'	179 (74.0%)	43 (20.1%)	174 (69.3%)	31 (17.1%)
ECG				
Normal	65 (26.9%)	87 (40.7%)	65 (25.9%)	75 (41.4%)
Atypical changes	68 (28.1%)	90 (42.1%)	71 (28.3%)	73 (40.3%)
Typical ischemic changes	109 (45.0%)	37 (17.3%)	115 (45.8%)	33 (18.2%)
Age (years)				
<70 years (in vignette 65 years)	77 (31.8%)	72 (33.6%)	71 (28.3%)	67 (37.0%)
70-80 years (in vignette 75 years)	102 (42.1%)	55 (25.7%)	107 (42.6%)	40 (22.1%)
>80 years (in vignette 85 years)	63 (26.0%)	87 (40.7%)	73 (29.1%)	74(40.9%)
Renal function				
No renal dysfunction	101 (41.7%)	52 (24.3%)	84 (33.5%)	59 (32.6%)
Mild to moderate renal dysfunction	80 (33.1%)	68 (31.8%)	92 (36.7%)	51 (28.2%)
Severe renal dysfunction	61 (25.2%)	94 (43.9%)	75 (29.9%)	71 (39.2%)
Previous CAD				
Yes	145 (59.9%)	91 (42.5%)	126 (50.2%)	94 (51.9%)
Persistent chest pain				
Yes	139 (57.4%)	81 (37.9%)	145 (57.8%)	67 (37.0%)
Risk factors‡				
No risk factors	73 (30.2%)	74 (34.6%)	79 (31.5%)	62 (34.3%)
One risk factor	77 (31.8%)	74 (34.6%)	80 (31.9%)	55 (30.4%)
More than one risk factor	92 (38.0%)	66 (30.8%)	92 (36.7%)	64 (35.4%)
Risk score outcome∞	n.a.	n.a.		
Low			32 (12.7%)	66 (36.5%)
Intermediate			163 (64.9%)	93 (51.4%)
High			56 (22.3%)	22 (12.2%)

† According to cardiologists' own hospital standards. ‡ i.e. diabetes mellitus, hypertension, hypercholesterolemia, smoking, and positive family history. ∞ Calculated risk according to risk score applied in cardiologist own practice (for instance GRACE or TIMI). ≈ Presented data concerns the number of vignettes in which cardiologists decided whether or not to perform a CA given a certain factor. For instance, for factor troponin: in vignettes where cardiologists decided to perform a CA in 74% troponin levels were elevated. Abbreviations: ca, coronary angiography; CAD, coronary artery disease; ECG, electrocardiogram; n.a., not applicable

8

General discussion

In this thesis several studies are presented that together aim to investigate the extent of guideline adherence in the management of patients diagnosed with non-ST-elevation acute coronary syndrome (NST-ACS), with emphasis on the use of cardiac risk scores (e.g. GRACE or TIMI risk score) in clinical practice. Another aim was to identify determinants for suboptimal cardiac risk score use. Furthermore, the importance of different components of clinical information, including risk score outcomes, on cardiologists decision-making regarding performing coronary angiography was studied. Quantitative and qualitative study designs have been used.

In this chapter, the main findings are presented in section 8.1 and subsequently discussed in section 8.2. In section 8.3 possible methodological issues are discussed, in terms of strengths, limitations, and generalizability of the study results. In section 8.4 implications for clinical practice and future research are outlined. Finally in section 8.5 conclusions are presented in light of the research questions.

8.1 Overview of main findings

8.1.1 What is the extent of guideline adherence in patients with NST-ACS?

The extent of adherence to international cardiac guidelines, i.e. the ESC and ACC/AHA guidelines, varied widely between studies included in our systematic review *(Chapter 2)*. Adherence rates between 5.0% and 95.0% were found for acute and discharge pharmacological care, and between 16.0% and 95.8% for performing coronary angiography (CA). Only a few studies looked into the use of different risk stratification methods (e.g. troponin measures, performing an ECG, use of cardiac risk scores), for which adherence rates were found varying between 34.3% and 93.0%. Lower guideline adherence was consistently found to be associated with poorer prognosis. Yet, none of the studies regarding the extent of adherence to risk stratification methods looked into this relationship.

In a cross-sectional multicentre study *(Chapter 3 and 4)* we further studied the extent of guideline adherence in NST-ACS care, but with specific attention to the use of validated cardiac risk scores in clinical practice. Data of 1788 patients discharged with a diagnosis of NST-ACS were analysed. Consistent with the findings from the systematic review, large variation in adherence rates was found. On average in 57.0% of the cases a cardiac risk score was documented in the patient's chart. For the thirteen hospitals included in the study, adherence rates ranged from 16.7% to 87.0%.

8.1.2 Which factors are associated with cardiac risk score use?

To find a possible explanation for the variation found in cardiac risk score use between hospitals, we studied the association between several clinical or contextual factors and the extent of guideline adherence. Factors derived from our systematic review *(Chapter 2)* were related to guideline adherence in the management of NST-ACS in general, and are therefore not further elaborated below.

Similar to previous literature [1-3] on the subject of influential factors (i.e. barriers or facilitators) in relation to the implementation of guidelines, factors associated with the extent of cardiac risk score use were either related to the guideline itself, the patient, the healthcare provider or the organization. With exception of some of the factors found to be related to the patient, all factors are derived from semi-structured interviews with 31 healthcare providers from 11 hospitals *(Chapter 5)*.

Guideline related factors

Five factors influencing cardiac risk score use were related to the risk score itself (Table 8.1). First, the lack of a clear clinical relevance of the risk score was an important influential factor. With clinical relevance referring to either proven benefits on a patient level in terms of a reduced risk of dying or myocardial infarction, or to benefits for clinical practice in terms of improved continuity of care. It was often mentioned by healthcare providers that a clear clinical relevance of the risk score would be a major facilitator, and would reduce resistance among its intended users. Hospitals with high percentages of risk score use, often incorporated risk score outcome categories (i.e. low, intermediate, high) in existing clinical pathways or protocols, and in that way made a direct link to treatment choices, which made the relevance of the risk score more pronounced. A lack of clinical relevance was either a reason not to use a risk score at all, or led to risk score use for administrative purposes only instead of as a guide in decision-making.

Second, the lack of a clear scientific evidence base, e.g. (quasi) experimental studies supporting the use of a risk score in terms of improved patient outcomes, made healthcare providers hesitant to base any treatment decisions on the outcome of the score. Risk scores were often used due to external pressure, but not actually influenced decision-making. Extrinsic motivations for cardiac risk score use mentioned by health care providers were for instance the fact that risk scores are strongly recommended in international clinical guidelines, or the use of risk scores being a performance indicator of the national quality improvement program (VMSzorg) adopted by different stakeholders (e.g. Dutch healthcare inspectorate or healthcare insurance companies).

Third, the complexity of the risk score was a frequently mentioned barrier. Not every risk score was perceived as user-friendly. For instance, the GRACE risk score [4,5] was experienced as highly complex in its use as it could not be calculated rapidly at the patient's bedside, but required the necessary information technology (IT) support which was not always present in every hospital or hospital-department.

Fourth, as IT support was often lacking in many organizations, healthcare providers experienced a high administrative burden and time loss associated with cardiac risk score use, which increased resistance to the use of these instruments in clinical practice.

Fifth, frequent updates of clinical guidelines was another barrier in risk score use. While practitioners were still in the process of implementing guideline recommendations of previous guideline versions in their own protocols or standards, new guidelines emerged with updated recommendations. This made it difficult to sustain cardiac risk score use over time.

Table 8.1 Factors related to the guideline

Guideline related factors	Direction of Adherence
(Lack of) Clinical relevance of guideline (i.e. benefits for patient and/or clinical practice)	↓↑
(Lack of) scientific evidence base	↓↑
Complexity of underlying algorithm of risk score	↓↑
Administrative burden / time loss	↓
Fast update of guidelines	↓

↓, lower guideline adherence; ↑, higher guideline adherence; ↓↑ associated with both lower and higher guideline adherence

Patient related factors

Several characteristics related to the patient were associated with risk score use (Table 8.2). In our patient chart review *(Chapter 3 and 4)*, six (out of 26 clinical factors) were significantly associated with cardiac risk score use ($p \leq 0.05$). Risk scores were more often used in obese patients (OR 1.49, 95%CI 1.03 – 2.15)[1] and in former smokers (OR 1.56, CI 95% 1.15 – 2.11). By contrast, risk scores were less likely being used among patients diagnosed with unstable angina compared to patients diagnosed with NSTEMI (OR 0.60, CI 95% 0.46 –

1 Abbreviations: OR, odds ratio; 95%CI, 95 percent confidence interval

0.77), in patients who were resuscitated when presenting in the hospital (OR 0.23, CI 95% 0.09 – 0.64), in patients with in-hospital heart failure (OR 0.46, CI 95% 0.27 – 0.76), and in patients with tachycardia (OR 0.45, CI 95% 0.26 – 0.75). In addition, in *Chapter 5*, healthcare providers questioned whether risk scores could cover the full spectrum of NST-ACS patients. Therefore they did not always trust or use the risk score, e.g. in case of patients with severe comorbidities or in the elderly.

Table 8.2 Factors related to the patient

Guideline related factors	Direction of Adherence
High age, cognitive impairment, immobility†	↓
Diagnosis of UA (versus NSTEMI)	↓
Tachycardia, in-hospital heart failure, in-hospital resuscitation	↓
Obesity, former smoker	↑

† factors are derived from interviews with healthcare providers, all other factors were significantly ($p \leq 0.05$) associated with cardiac risk score use in multivariable analyses.
↓, lower guideline adherence; ↑, higher guideline adherence

Healthcare provider related factors

Several factors influencing cardiac risk score use were related to the healthcare provider (Table 8.3). In our interview study the importance of intrinsic motivations for change versus external pressure became more clear. *First*, the most common intrinsic motivation mentioned was the need for a more uniform approach in treatment practices for patients presenting with suspected NST-ACS in hospital. Cardiac risk score use indeed led to more uniformity in treatment practices and as a result healthcare providers believed that this enhanced patient safety, efficient resource use, and a more rapid identification of high risk patients who would benefit most from invasive and timely treatment. *Second*, cardiac risk scores were implemented for educational purposes, and created more awareness among less experienced physicians for assessment of a patient's risk of re-infarction or death. *Third*, risk scores were considered of value for scientific research, in which risk scores were used by physicians to study severity of illness among their own population of patients. However, regardless of a healthcare provider's motivation for cardiac risk score use, users of risk scores feared for overregulation of the process of NST-ACS care. Healthcare providers mentioned that the risk of cardiac adverse events could possibly be overestimated and that treatment policies should thus not be solely based on a risk score outcome.

The scores were in the majority of cases used as a guide in decision-making, combined with conventional risk assessment methods (e.g. troponin measures), and were used to decide on appropriate treatment, to guide admission, or to enhance throughput of patients to other hospital departments. Furthermore, the score was used as an objective support system to quantify a physician's own risk assessment, in order to confirm their assumptions regarding a patient's risk and/or to justify their chosen treatment plan. However, it was frequently mentioned by healthcare providers that if a clear clinical relevance and/or intrinsic motivation for change was lacking, cardiac risk scores were solely used for administrative purposes to meet demands from third parties or stakeholders. In that case implementation of cardiac risk scores was mainly driven by external pressure, and this increased resistance instead of commitment to cardiac risk score use. Although external pressure led to resistance, it also accelerated the use of risk scores in practice. The performance indicators mentioned in the national quality improvement program (VMSzorg) stimulated the use of cardiac risk scores, and partly due to its obligatory character, all hospitals aimed to follow the recommendations of the improvement program. Just as the corporation of cardiac risk scores in the ESC guidelines accelerated the implementation process in several hospitals. However, several healthcare providers questioned whether hospitals would continue to use cardiac risk scores in daily practice without this external pressure being present.

Other factors that were mentioned by healthcare providers as barriers in using or implementing a risk score in practice were: a lack of familiarity, lack of knowledge, lack of agreement, older age, and more years of work experience. In the latter case, it was suggested that older, more experienced, cardiologists were more likely to base treatment decision on their own gained knowledge over the years, instead of using risk scores, than less experienced physicians.

Table 8.3 Factors related to the healthcare provider

Healthcare provider-related factors	Direction of Adherence
Intrinsic motivations for change	↑
Extrinsic motivations for change	↓↑
Lack of clinical relevance	↓
Physician's characteristics: level of work experience	↓
Lack of familiarization with new practices	↓
Lack of knowledge	↓
Lack of agreement / commitment	↓↑

↓, lower guideline adherence; ↑, higher guideline adherence; ↓↑ associated with both lower and higher guideline adherence

Organization related factors

Although in our patient chart review *(Chapter 4)* we did not find a significant association between characteristics of the organization (i.e. the presence of on-site revascularization facilities (i.e. CA, PCI and/or CABG) and a hospitals' teaching status) and cardiac risk score use, from the interviews *(Chapter 5)* with healthcare providers several organization-related factors emerged that were either seen as facilitators or barriers (table 8.4).

The absence of necessary resources, in the case of cardiac risk scores the availability of the necessary IT support, was a major influential factor in either enhancing or decreasing the use of risk scores in practice. The same accounted for the available management support, and the priority that was given by hospital management to the use of cardiac risk scores in patient management. Hospitals in which it was for instance possible to incorporate a risk score calculator in existing electronic hospital systems, and hospitals in which staff-physicians or other healthcare providers actively supported and emphasized the importance of using such an instrument in practice, had higher rates of cardiac risk score use. Furthermore, in these hospitals strategies such as frequent reminders and data feedback were used to enhance cardiac risk score use, leading to more intrinsically motivated users of cardiac risk scores. In hospitals where this kind of support was lacking or was absent, resistance among users had the over hand, and risk scores were only used to – as mentioned before – comply with demands of external parties.

Besides a lack of resources, other barriers that were frequently mentioned by healthcare providers were: high workload, lack of time and the fast rotation of staff. The latter made it difficult to sustain cardiac risk score use, as frequent rotation of medical interns or medical residents led to a knowledge deficit, and continuously demanded education and training by staff-physicians. Time constraints and a high work load hampered physicians to get familiarized with the guideline recommendations, and in that way led to a knowledge deficit.

Table 8.4 Factors related to the organization

Organization-related factors	Direction of Adherence
Lack of resources: IT support	↓↑
Management support / priority	↓↑
High workload	↓
Lack of time	↓
Frequent staff rotation	↓
Unexpected circumstances at staff level	↓

↓, lower guideline adherence; ↑, higher guideline adherence; ↓↑ associated with both lower and higher guideline adherence

8.1.3 What is the importance of various types of clinical information, including cardiac risk scores, in deciding on the management of patients with NST-ACS?

Cardiac clinical guidelines recommend that physicians make use of multiple clinical factors when deciding on performing coronary angiography in NST-ACS patients [6,7].
However, there is little insight in how physicians' weigh different clinical information when deciding on the treatment of these patients, and to what extent cardiac risk score instruments are part of the decision-making. A nationwide survey was conducted *(Chapter 6 and 7)*, in which cardiologists were asked to decide for clinical vignettes whether or not to perform CA. Cardiologists were divided in two groups, with one group receiving clinical vignettes without risk score information present, and the other group receiving vignettes with risk score information present. In both groups decision-making was mainly driven by three sources of clinical information, namely troponin levels, ECG changes and a patient's renal function. Cardiologists were more likely to perform CA in patients with elevated troponin levels and in patients with typical ischemic changes on the ECG. In patients with severe renal dysfunction cardiologists were less likely to perform CA. Persistent complaints of chest pain, previous coronary artery disease and presence of risk factors hardly influenced cardiologists' decision-making. Since effects of risk score were highly associated with age, no firm conclusions could be drawn about the effect of risk score or age separately on cardiologist decisions. However, looking at a combined factor of age and risk score, a significant association was found with performing CA, with cardiologists being more hesitant to perform CA in elderly patients with high risk score according to a validated risk score, than in younger patients with intermediate risk.

To summarize:

- Adherence to cardiac guideline recommendations in the management of NST-ACS varies widely, where rates for cardiac risk score use may be less than 25.0% or more than 80.0%.
- The extent of guideline adherence is associated with several factors, and can be summed under the following categories: risk score, patient, healthcare provider and organization. Factors were studied more extensively in a qualitative study in which a division between intrinsic motivations and extrinsic motivations for cardiac risk score use became clear, with the type of motivation being determinative for whether or not the risk scores are actually adopted by healthcare providers and subsequently its use is sustained in practice.
- Physicians primarily based their decision-making regarding performing coronary angiography on three sources of clinical information, with elevated troponin levels and typical ischemic changes on the ECG making cardiologists more likely to perform CA, and severe renal dysfunction making cardiologists less likely to decide on CA.

8.2 Interpretation of main findings

In NST-ACS, higher rates of guideline adherence are associated with improved patient outcomes, in terms of death and/or re-infarction [8]. Evidence based practice, in which care is provided according to the latest scientific evidence, i.e. by adhering to the available clinical practice guidelines, seems therefore obvious. However, our study results show a large variation in adherence rates in NST-ACS care. The same holds for the application of cardiac risk scores in clinical practice where a large variation in cardiac risk score use was seen between hospitals.

Over the years, several studies have been conducted regarding the accuracy of clinical prediction models, like for cardiac risk scores, in risk assessment and clinical decision-making [9-11]. These studies demonstrated that well-developed and extensively validated risk scores are objective and can more accurately weigh a large number of factors simultaneously than a physician can without support of such a model. In several studies it is demonstrated that using risk scores in addition to conventional risk assessment (i.e. clinical judgement) for decision-making in NST-ACS is superior to conventional risk assessment alone [4,12-17]. Furthermore, in the latest ESC and ACC/AHA guidelines the use of risk scores in risk assessment and decision-making regarding appropriate treatment is a class I[2] recommendation [6,7]. Although the available scientific evidence summarized in the clinical guidelines speaks for a more consistent use of risk scores in daily practice, our study results show that a large variability in use still exists. Profession-wide there is an agreement that risk scores are beneficial for clinical practice and should be used, this reflected in recommendations in available evidence based clinical practice guidelines for the management of NST-ACS. However, in clinical practice, at the point of care, there seems to be a lack of agreement and in some cases a lack of intrinsic motivation to use risk scores when deciding on the treatment for an individual patient.

Looking at the process of decision-making explained by Kahneman [18,19], physicians' (i.e. cardiologists') decision-making seems to be mainly based on the intuitive system, i.e. highly depended of previously gained experience and a person's own clinical assessment of the situation, in combination with a common focus on a limited number of clinical factors. When cardiologists are presented with simulated patient cases of NST-ACS, and were asked to decide on performing coronary angiography or not, they tended to primarily focus on a limited number of factors, being troponin levels, ECG changes and a patient's renal status. Furthermore, a treatment risk paradox seemed apparent. In clinical vignettes representing

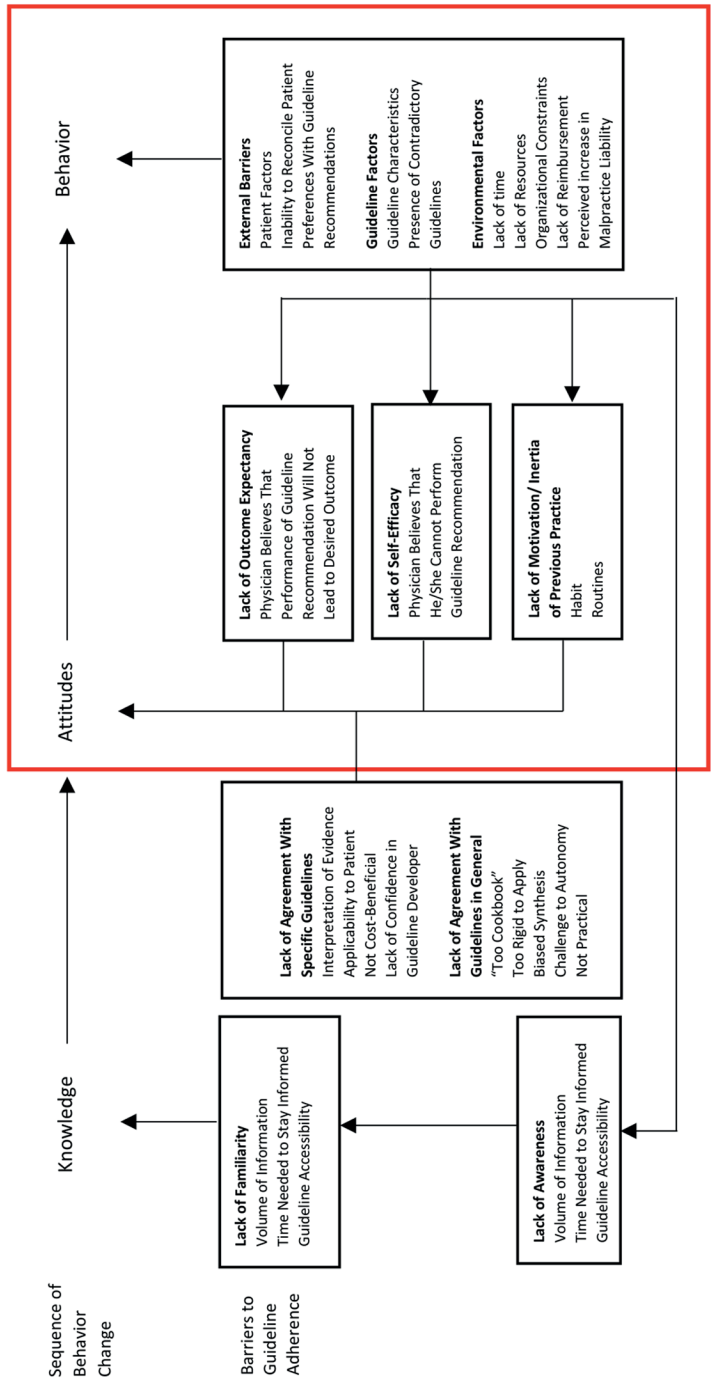
2 Class I recommendation refers to: 'the condition in which there is evidence or general agreement that a certain procedure or treatment is beneficial, useful, effective, and thus recommended/should be performed'[6,7].

high risk NST-ACS patients (i.e. with severe renal failure, or both a high age and high risk of adverse events according to a validated risk score) cardiologists were hesitant to perform CA, compared to patients without such characteristics. Previous literature regarding the treatment risk paradox, showed similar results, with physician's decision-making being mainly driven by an assessment of certain factors, and possibly neglecting others [13,15,16]. In high risk patients, such as the elderly or patients with comorbidities, cardiologists tended to underestimate the potential benefits and overestimate the risk of harm from invasive therapies, consequently prescribing or performing more conservative treatments [20-22]. Although high risk patients have a higher prevalence of contra-indications for several guideline recommended treatments, providing cardiologists with grounded reasons to deviate from the guidelines, a treatment-risk paradox is still apparent after a correction for the presence of these contra-indications [23]. Possibly, the presence of factors related to the healthcare provider (e.g. cardiologist) or organization is a reason for the perpetuating treatment risk paradox and variation in application of cardiac risk scores.

Wallace et al. [24] propose a four phase framework when implementing clinical prediction models/risk scores in clinical practice. After determining if factors included in the risk score are clinically sensible and appropriate (phase 1) it is recommended to determine the acceptability of the risk score among the target group by making an assessment of existing barriers and by determine ways on how to integrate the risk score into the daily workflow of the target group (phase 2). This is recommended before the actual impact of the risk score is measured (phase 3) and subsequently implemented in daily clinical practice (phase 4). In cardiac risk score use, several factors were identified that possibly explain the variation in adherence rates between hospitals regarding cardiac risk score use. These factors are consistent with previous literature regarding barriers for guideline adherence and can be divided in the following categories: guideline-, patient-, healthcare provider-, and organization-related factors [1-3]. Most barriers in cardiac risk score use were found to be related to the healthcare provider or the organization, and were derived from detailed interviews with healthcare providers. These major barriers comprised, among other, the lack of a strong scientific evidence-base and clinical relevance (i.e. impact studies), lack of motivation (i.e. intrinsic versus extrinsic), and lack of necessary resources in combination with complexity of the risk score (i.e. IT and management support). Below, the major barriers found to be related to cardiac risk score use will be elaborated on, and put in a theoretical perspective.

8.2.1 Barriers for cardiac risk score use

In the late nineties Cabana and colleagues [3] after a large systematic review developed a framework in which major barriers for physicians to adhere to clinical guidelines are presented. The different barriers were summarised in seven categories related to the different stages of behaviour change: i.e. physician's knowledge (lack of awareness, lack of familiarity),



Source: Cabana, MD, Rand CS, Powe NR, Wu AW, Wilson MH, Abboud, PA & Rubin HR. Why don't physicians follow clinical practice guidelines? A framework for improvement. JAMA 1999;282:1458-1465.

Figure 8.1 Framework of Cabana et al. [3]: barriers to physician adherence to practice guidelines

attitude (lack of agreement, lack of self-efficacy, lack of outcome expectancy, inertia of previous practice) or behaviour (external barriers, including patient-, environmental- and guideline- related barriers) (Figure 8.1). Note that physician characteristics, such as age, gender, background, and so on, are not included in the framework, because only factors that could be influenced and subsequently changed were considered.

Knowledge

Cabana et al. found that a lack of awareness and a lack of familiarity with the guideline, among others due to the amount of information in clinical guidelines, time needed to stay informed, and accessibility of the guideline contributed to a lack of knowledge. In the management of NST-ACS, there is no doubt that hospitals and cardiologists included in the different studies were aware and in great extent familiar with the content of the cardiology guidelines (e.g. ESC and ACC/AHA). However, the fast update of guidelines and frequent staff rotation of junior physicians hampered proper implementation of the scores, and made it difficult to sustain cardiac risk score use in practice. Especially as these younger physicians made up a great part of the target group i.e. (potential) direct users of cardiac risk scores in practice.

Attitudes

Cabana et al. summarized several barriers that influence physicians' attitudes towards following guideline recommendations.

First, a lack of agreement with guideline (recommendations). In the management of NST-ACS, only limited (quasi-) experimental or prognostic observational studies regarding the association between risk score use and patient outcomes have been conducted. This made cardiologists and other healthcare providers doubt the value and accuracy of these scores for clinical decision-making. Cabana et al. [3] bring up the following in their systematic review: '…since physicians see patients individually, they may not discern success at the population level. Overlooking population-level successes can negatively influence outcome expectancy and lead to nonadherence'. This also seems to be the case in risk score use in NST-ACS patients. Although clinical guidelines summarize effects on a population level of risk score use and recommend the use of these instruments in practice, this belief is not (fully) shared by healthcare providers. Furthermore, previous literature suggested that physicians might doubt whether the study populations in which the discriminative ability of the risk scores are tested properly reflected real life population of patients. Therefore a patient's actual risk may differ substantially from the risk calculated in the study with the population-based risk score. As a result physicians rather base decision-making on their own medical knowledge [25,26]. The reluctance of using risk scores due to a lack of a sound scientific evidence base became apparent in our qualitative interview study, where also the oversimplification of the process of risk assessment was brought up, i.e. management of complex clinical cases being

reduced to a single risk score. Physicians were concerned that overemphasis on risk scores may discourage good clinical judgement. This, together with the growing demands by third parties to use risk scores in clinical practice, led to resistance among its intended users. This oversimplification of the process of risk assessment is being described in Cabana's framework as 'cookbook medicine' and indeed associated with lower guideline adherence.

Second, lack of agreement was highly related with lack of clinical relevance. Clinical relevance is in Cabana's framework explained as lack of outcome expectancy, i.e. lack of belief of a physician that if the guideline (recommendation) is followed it will make a difference in terms of patient outcomes. The absence of clear benefits on a patient level of cardiac risk score use (i.e. death or re-infarction) or for clinical practice (i.e. improved continuity of care) made cardiologists doubt the added value of using a cardiac risk score. Interestingly, in a qualitative study with 68 general practitioners (GPs) based in Germany, it was found that GPs doubt the accuracy of risk scores except in the case of management of coronary heart disease [25]. In this patient population the added value of risk scores became clear because the scores supported GPs to differentiate better between patients in terms of risk and appropriate treatment. However, in our qualitative study healthcare providers mentioned that this is only the case if risk scores are integrated in existing pathways where treatment choices (in terms of performing coronary angiography or not) are depending on a patient's level of risk being partly determined by the use of cardiac risk scores.

Third, Cabana and colleagues found that a lack of motivation, i.e. the readiness for change, was a major barrier in guideline adherence. In cardiac risk score use the reason for change influenced the extent of cardiac risk score use. Extrinsic motivation i.e. external pressure, rather than intrinsic motivation accelerated implementation in Dutch hospitals. However, this primarily led to use of cardiac risk scores for administrative purposes instead of 'actual' risk score use. In case adoption of a risk score was driven by intrinsic motivations, several benefits in risk-assessment, and additionally in policy-making, education, and research were experienced which enhanced cardiac risk score use in practice. Stimulating intrinsic motivation of healthcare professionals has been described before as a successful approach to change clinical practice [27].

Behaviour

Cabana et al. [3] describe in their systematic review that behaviour, i.e. 'using a risk score or not' can be changed without influencing a physician's knowledge or attitude, but as a consequence behaviour change will be less sustainable. This accounts for risk score use as well. Several external barriers were found that influenced physician's behaviour. As explained before, in hospitals were extrinsic motivations had the overhand risk score use was solely used for administrative purposes and healthcare providers did not believe that risk scores use would

be sustained over time. In figure 8.1 it can be seen that the persistence of external barriers can negatively influence physician's outcome expectancy, self-efficacy (i.e. a physician's belief that he/she can actually perform a certain behaviour), or motivation. Several factors were found that limited healthcare providers in cardiac risk score use and were mainly related to the guideline or the organization. A major barrier was, for instance, the complexity of the risk score in combination with a lack of support or absence of necessary practical resources. In the clinical guidelines, the GRACE risk score is highlighted as being most accurate and extensively validated [4,5]. Hospitals included in our chart review, and healthcare providers participating in the qualitative study, predominantly adopted the GRACE risk score as their main instrument to stratify patients in risk classes due to the fact that this risk score had the largest scientific evidence base and was recommended by the guidelines. However, healthcare providers perceived the GRACE risk score as complex in its use, especially without sufficient IT support. This often contributed to an already high workload of healthcare providers, resulting in resistance and lack of agreement. Furthermore, as mentioned before, cardiologists decision-making regarding performing coronary angiography was primarily based on a limited number of factors, with no conclusive result regarding the impact of risk score outcomes on decision-making.

Other

In Cabana's framework several other barriers are mentioned that were not derived from any of our studies. This concerned a physician's self-efficacy (attitude). A lack of self-efficacy is mainly a barrier when physicians have to adhere to guideline recommendations concerning preventive health education or counselling strategies where it is aimed to change patient behaviour (e.g. quit smoking counselling), which is not the case in the application of risk scores. Furthermore, cardiac risk scores consist mainly of factors that physicians are familiar with from their own clinical practice and education. It does not require any new knowledge or skills.

Another barrier found in Cabana's framework, was the influence of patient preferences towards the guideline recommendations (external barriers: guideline). The inability to reconcile patient preferences with guideline recommendations, and possible resistance of patient's towards specific guideline recommendations, is a frequent mentioned barrier. However, the application of risk scores is not directly related to the patient in terms of an acquired behaviour change. This possibly explains why patient's preferences was not found to be associated with cardiac risk score use. Patient's preferences, for instance not willing to be invasively treated, could be a reason for the physician to deviate from the guideline, and makes the calculation of a risk score unnecessary.

Last, concerns about legislation of guidelines and lack of financial incentives were mentioned as external barriers in Cabana's framework. As the application of risk scores was part of a national

improvement program, and all hospital boards were obligated to follow the recommendations of the improvement program, resources in terms of finances were possibly not an issue, just as concerns about legislation of the guideline(recommendations). However, healthcare providers did mention several other resource constraints, such as a lack of IT support.

8.3 Methodological issues

There are several strengths and limitations related to the studies included in this thesis that should be taken into account.

8.3.1 Strengths

Use of multiple methods to collect data

The use of different research designs made it possible to gain a deeper understanding of the use of cardiac risk scores in clinical practice. Thus, besides insight into the extent to which they were actually used in practice, we also gained insight into the motivation for use, possible influential factors and the importance of risk scores for cardiologists' decision-making. Quantitative methods made it possible to determine the frequency of cardiac risk score use, and variation in its use. The interview study and vignette study made it possible to gather more contextual information that helped to interpret the results and to explain the variation of cardiac risk score use in practice.

Furthermore, several actions were taken to present an as reliable as possible reflection of the current standards of care in the management of NST-ACS. For instance, all available evidence regarding guideline adherence in NST-ACS care was systematically assessed, extracted and analysed independently by two researchers. Next, the patient chart review was performed in multiple hospitals, resulting in a large and representative data set of NST-ACS patients. In addition, the interview study was theory driven in which topics of the interview guide were based on a thorough assessment of available literature on guideline-implementation. Furthermore, the clinical vignettes were developed in accordance with an expert panel of cardiologists and a proper design was developed with the aid of statistical software. These aspects increased the credibility of the study results.

Representative dataset of NST-ACS patients in the Netherlands

Selection bias, in which patients are systematically excluded for instance because of their gender, age or present co-morbidities, is a common concern in clinical trial populations, but also in registry studies, and may have important implications for quality assessment [28,29]. Independent researchers therefore performed the random enrolment of patients

in our retrospective chart review study, instead of letting the treating physicians determine eligibility. In this way, we tried to minimize the chance of selection bias, thereby preventing misrepresentation of hospital performance. (Independent) cardiologists or cardiology residents employed in the participating hospitals were often consulted to verify data found in medical records, for instance in case of doubt about a patient's final diagnosis.

8.3.2 Limitations

Possible underrepresentation of actual adherence rates

The studies included in our systematic review most often concerned registry studies, which, as explained above, involve risk of selection bias. In the majority of included studies in our systematic review information on guideline adherence was prospectively collected. In some studies data was retrospectively derived from patients' medical records. This was also the method of data collection of our cross-sectional study. Data recorded in the patient's charts were not initially gathered with the purpose of measuring quality of care i.e. the extent of guideline adherence. As a consequence, information can be absent or missing, incorrectly registered or specific contra-indications providing a legit reason to deviate from the guidelines might be overlooked, as it is known that contra-indications are not always properly documented by attending physicians [30]. Consequently, our estimation of guideline adherence rates are less accurate than when data were collected prospectively. Guideline adherence rates in the systematic review or in our cross-sectional study may underestimate actual adherence rates in clinical practice. However, the impact on our conclusions regarding the extent of guideline adherence is little, as the variation in adherence rates is so large.

Representation of a real-life clinical situation

Decision-making was studied in an experimental setting, in which clinical vignettes representing actual patients were used. Although clinical vignettes are, instead of actual observations in practice, a valid approach to measure decision-making, it does not fully represent actual clinical practice. The cardiologists that participated in the study were for instance not able to observe their patients, did not experience any time-pressure, and were presented with a limited amount of clinical information. Decisions made on the basis of the vignettes can therefore be different from decisions made in actual clinical practice.

8.3.3 Generalizability

Although we put a lot of effort in selecting/recruiting a large cohort of NST-ACS patients for the patient chart review study, we approached all cardiologists registered in the Dutch directory of physicians for the clinical vignette study, and we interviewed a large group of healthcare providers employed in several Dutch hospitals, there are some limitations that may affect generalizability of the study results to other Dutch hospitals and/or countries.

Highly motivated cohort of participants

In all studies participants (either being hospitals or healthcare providers) were highly motivated to participate in scientific research, which could have influenced the generalizability of the different study results. However, in our patient chart review we collected data in multiple hospitals (n=13) and were able, in statistical analysis, to correct for random hospital effects. Also, in our qualitative study we continued interviewing until saturation was reached i.e. additional participants were interviewed up to the point no new information occurred. In our clinical vignette study, however, despite frequent reminders the non-response was unexpectedly high. Nevertheless, several markedly significant associations were found, which provided further insight in decision processes of cardiologists. Furthermore, several of our study results are comparable with previous (international) studies which supports the generalizability of the results. The descriptive character of all of the studies included in this thesis make the results informative for all hospitals/healthcare providers who want to implement a risk score, or enhance cardiac risk score use in practice.

8.4 Implications for clinical practice and future recommendations

8.4.1 Implications for future research

Study the implementation of guideline recommendations

In the field of implementation science it is recommended that more research should be conducted regarding how to implement the evidence in the guidelines in practice [1,27]. The same holds for the management of NST-ACS, were we recommend to study the feasibility of the implementation of the ESC and/or ACC/AHA guideline recommendations in practice. Although clinical guidelines ensure a certain standard of care, and decrease variation in care, they seem difficult to successfully implement in practice. Moreover, factors related to the healthcare provider or the organization and factors related to the guideline itself were found that influence the extent of adherence. Cardiologists mentioned, for instance, in our interview study that it is difficult to keep up with the publication of new scientific research presented in updated versions of the clinical guidelines. To illustrate, for the design of the vignette study the content of the guidelines, available risk scores and other relevant resources in relation to performing coronary angiography were reviewed. Over 100 factors were found to be related with the decision to perform coronary angiography or not. A cardiologists thus has to review over 100 possible factors in a short period of time to come to a thorough decision regarding appropriate treatment. This is of course not feasible in practice. To successfully implement the guidelines in practice – including recommendations regarding cardiac risk scores use – it is necessary to gain more knowledge regarding which (combination of) strategies are effective in overcoming certain barriers. In that way future quality improvement initiatives can select effective strategies and tailor these to the present barriers.

Study the impact of risk score use on patient outcomes

It is recommended that (more) studies are conducted in which the impact of risk scores on patient outcomes or processes of clinical care is measured. Demonstrating that using a risk score in addition to a physician's own risk assessment (versus not using a risk score) is associated with improved processes of clinical care or patient outcomes should diminish a healthcare providers resistance and lead to an increase in risk score use. A randomized controlled trial (RCT) is most optimal, a good alternative (that is also less time-consuming) is a controlled before-after design in which outcomes are measured before, during, and after using a cardiac risk score compared to outcomes of a control group in which usual care is provided [24]. Impact analyses are subjected to similar sources of bias, just as regular RCTs are, and concern randomization, blinding, sample size, and so on. An important pitfall lies the way the instruments are introduced and implemented in practice. Low usage rates of risk scores, can relate to several barriers that exists that are not thoroughly assessed and addressed before implementation [24].

8.4.2 Implications for clinical practice

Prevention of practice variation

Given the indication that risk score use improves the processes of care and studies indicating that risk assessment is more accurate when also using a risk score it is recommended that healthcare providers involved in the management of NST-ACS patients use validated cardiac risk scores as additional support systems in their clinical decision-making. Note, we want to point out that risk scores are never meant to replace clinical judgement, or that not using a risk score is perceived as being equal to lower standards of (quality) of care. It is preferable that the scores are used as a tool to improve continuity of care, increase standardization of care, and subsequently reduce any unwarranted practice variation. With 'unwarranted' referring to practice variation that cannot be explained by characteristics of the patient (e.g. co-morbidities, type of illness or preferences), but for instance by characteristics related to the healthcare provider or organization, which seems to be mainly the case in cardiac risk score use [31]. Although physicians are continuously (implicitly) assessing complex clinical cases, the provided care is often subjected to the knowledge, attitude or behaviour of the physician, instead of available scientific evidence. Patients submitted to hospitals with underlying cardiac conditions are for instance more subjected to (unwarranted) practice variation, with negative consequences in terms of patient safety [32]. Wide-spread dissemination of risk scores can be a possible solution, but asks for implementation trajectories in which all present barriers are taken into account.

Implementation of risk scores

Several factors were found that are indicative for the extent to which risk scores will be used in clinical practice. Ideally, it is recommended that risk scores are used in addition to conventional risk assessment (i.e. clinical judgement), however several barriers were found that decreased cardiac risk score use in clinical practice. These barriers were mainly related to the healthcare provider and the organization, in terms of a skeptic attitude or resource constraints. To successfully implement risk scores in practice, and stimulate actual use, it is necessary that implementation strategies are targeted towards these present barriers and intrinsic motivation of healthcare providers is addressed (Box 8.1). It is recommended that individual cardiology departments make an assessment of local barriers, provide the necessary support and resources to integrate risk scores in existing clinical pathways or information systems, and in that way sustain cardiac risk score use over time. This undertaking also counts for future qualitative improvement initiatives. In addition, it is recommended, although more research on this topic is needed, to use a multifaceted implementation strategy, tailored to present barriers, to implement risk scores in practice and in that way enhance implementation success [2]. Grol [27] recommend a 5-step systematic approach towards implementation and achieving change in practice, which is elaborated on in Box 8.1 within the framework of enhancing cardiac risk score use.

Monitoring risk score use

It is recommended that hospitals systematically document risk score outcomes, associated treatment decisions, and patient outcomes in patients' electronic records. This to assess the extent to which cardiac risk scores are actually used in clinical practice. Note, before monitoring, it is recommended to carefully determine which information from the guidelines is used for reflection upon the quality of care and providing feedback. To monitor actual risk score use, it is recommended to use electronic health care systems. This to better grasp the interaction between the daily workflow of a physician's practice, the necessary tools and the available evidence [37]. This necessary IT support should be provided in combination with data feedback, to prevent (more) work load for individual users, but resulting in performance improvements [37]. A good example are systems designed according to the principles of intermountain health care, in which information systems of hospitals are adapted to, and integrated in, daily health care processes, which makes continuous monitoring of quality standards on a department level possible [38]. Results are promising, for instance in the field of cardiology an increase in adherence rates regarding the prescription of discharge medications and improvements in clinical outcomes was found [39].

Box 8.1 Suggestion for implementation of risk scores in practice, following the 5-step approach of Grol [27]

Step 1 – Develop a change proposal
The first step is to develop a proposal for changing clinical practice. To increase adoption of a cardiac risk score by the target group it is important that the proposal is based on sound clinical evidence, and that any expected outcomes related to cardiac risk score use in clinical practice are clearly defined. This will increase intrinsic motivation of users regarding the use of these instruments in practice. Benefits of cardiac risk score, related to the process of care in terms of improved continuity of care or risk-assessment, can be stipulated on. Just as the evidence summed in the latest cardiac guidelines that all physicians tend to adhere to. This can be achieved by employing a combination of single implementation strategies such as reminders, feedback and the use of 'key' influential persons that can function as champions or opinion leaders.

To diminish any scepticism among healthcare providers regarding the additional benefit of risk scores for clinical practice, impact studies should be conducted and results should be disseminated among the target group. Furthermore, the risk score should be easy to use, and provided to its users in an accessible format, and in such a way that the score can be adapted to local standards. This asks for the necessary resources provided by the management, such as IT support. It is recommended that the risk score is integrated in existing pathways or digital support systems that follow daily clinical practice closely. For instance, an app which makes it possible to calculate a risk score next to a patient's bedside. Another important aspect at this stage of implementation is the way in which the risk score is introduced to the target group. Preferably by champions or opinion leaders, that have the respect of their peers.

Step 2 – Identify obstacles to change
The second is to make a thorough assessment of existing barriers related to the healthcare provider or organisation. An understanding of the problems that the target group will experience with the change is essential, and can differ among members of the target group. One person can be ready for change, where another is still considering change and not yet ready for concrete actions [33]. Actual change can be enhanced by taking away or minimalizing any existing barriers. In case of cardiac risks scores, major barriers concern the adoption (e.g. negative attitude of healthcare provider) and implementation (e.g. lack of necessary resources) of the scores (see Chapter 8.2.1).

Step 3 – Link intervention to obstacle
In the third step implementation strategies are selected that tackle the present barriers. To sustain cardiac risk score use over time, it is recommended that future quality improvement initiatives make use of a multifaceted implementation strategy. Although evidence regarding the effectiveness of multifaceted implementation strategies over the use of single implementation strategies is sparse and inconclusive [34,35], a systematic review summarized several studies in which a combination of two or more single implementation strategies appear to have a greater impact [2]. It is important to select strategies targeted to improve healthcare provider's attitude and intention to change and thereby improving adoption of the scores by the target group (e.g. cardiologists). In addition, the success of the strategy is often depended on the setting in which it is employed. For instance, in hospital A, physicians are sceptical towards the use of risk scores in practice (Barrier: physician's knowledge and attitude). The use of champions (staff physicians emphasizing the importance of risk score in practice) and active management support can be important strategies in creating awareness for the additional benefits of risk score use in clinical practice. In contrast, in hospital B, physicians are willing to use

Box 8.1 Suggestion for implementation of risk scores in practice, following the 5-step approach of Grol [27] (continued)

cardiac risk scores, however they experience several barriers related to the organization, such as lack of IT support or lack of management support, which decreases the willingness and prevents them from using the risk scores in practice (Barrier: external factors/physician's behaviour). This situation asks for different implementation strategies than in hospital A. Thus, a thorough assessment of present barriers before implementation is important to achieve successful implementation of risk scores in clinical practice. In addition, strategies that require active participation of the target group and that are closely related to clinical decision-making, i.e. are more integrated into the process of health care delivery, appear to be most successful [36]. Strategies that can be considered, are audit & feedback, reminder systems, monitoring, opinion leaders.

Step 4 – Develop a plan
In the fourth step the strategies are planned in terms of concrete activities for the short- and long-term. It is recommended not to use all the strategies at once, but in a series of activities, the effects of which can directly be monitored, and used for data-feedback to the target group (e.g. cardiologists). In cardiac risk score use, it is important to first make sure that all necessary resources are provided. Even if cardiologists are motivated to use risk scores in practice, the presence of barriers that hamper the use of the scores in daily practice results in a rapid decrease of motivation. Thus, necessary IT and management support should be provided. After that, users can be educated about the use of the risk scores thus creating awareness of the benefits of the risk scores in practice. Opinion leaders can be used to emphasize the importance of using the risk scores.

Step 5 – Carry out the plan and evaluate progress
The fifth step consists of continuous evaluation which is of utmost importance to sustain cardiac risk score use over time. Furthermore, changes can occur over time: new barriers that arrive, or changes within the target group. Possibly new interventions have to be selected and the plan should be adapted. Close monitoring of the implementation process is necessary.

8.5 Conclusion

The 2015 ESC guidelines state that '*In NST-ACS, quantitative assessment of ischemic risk by means of scores is superior to the clinical assessment alone*'. This statement, however, is not necessarily shared by healthcare providers at the point-of-care. Although cardiac risk scores are extensively validated in large cohort studies, and even in a few studies it was found that risk scores are superior to clinical assessment by physicians alone, their use in practice is relatively modest, and large variation in risk score use between hospitals exist. In addition, in a cohort of cardiologists, instead of multifactorial risk assessment as recommended by the guidelines, decision-making was primarily driven by a limited number of clinical factors.

Cardiac risk scores, however, are never meant to replace a physician's risk-assessment and decision-making regarding appropriate treatment. Not every patient meets the expectations of the guidelines in terms of risk/benefit ratio of a certain procedure, and in that case physicians have the task and responsibility to deviate from the guideline recommendation(s). However, the variation in guideline adherence and risk score use in the management of NST-ACS is too large to presume that in every patient case there were legit reasons/contra-indications to deviate from the guidelines. The care for patients with NST-ACS thus may be inadequate in terms of standardization, with as a result that not every patient is treated according to the latest scientific standards. Consequently, patients could be subjected to unnecessary therapies, or in the worst scenario experience adverse events such as re-infarction or death. It is therefore recommended that risk scores are used, *in addition to* conventional risk assessment. In that way clinical judgement, i.e. implicit decision-making based on clinical experience (subjective risk assessment), and quantitative judgement, i.e. decision-making by using risk scores (objective risk assessment) can complement and enhance each other.

Several barriers for cardiac risk score use were found, that can explain the large variation in adherence rates, and complicates the implementation of risk scores in daily practice. These barriers are related to the risk score itself, the patient, the healthcare provider and/or the organization. With emphasis on the latter two. Healthcare providers knowledge and attitude was, for instance, negatively influenced by a lack of agreement with the use of risk scores due to a lack of scientific evidence or clinical relevance of the risk score, in combination with barriers related to the risk score (complex in its use) or the organization (lack of necessary resources). As a result, instead of risk score use being mainly driven by intrinsic motivation for change, risk scores were implemented due to external pressure and consequently often used for administrative purposes only and did not actually affected decision-making regarding appropriate treatment. By contrast, healthcare providers that were intrinsically motivated to use cardiac risk scores in practice and received the necessary support, experienced benefits in for instance risk assessment and continuity of care.

Further research, regarding the impact of risk score use on patient outcomes is recommended to accelerate the implementation of these scores in practice. When implementing these scores in practice, a multifaceted implementation strategy, tailored to present barriers and in which intrinsic motivations are stimulated and the necessary resources are provided is recommended.

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Summary

Evidence-based risk assessment is of utmost importance for selection of the optimal management strategy in non-ST-elevation acute coronary syndrome (NST-ACS) patients. International cardiac clinical guidelines recommend that decision-making of physicians, regarding appropriate treatment, should include multifactorial risk assessment, i.e. taking into account multiple clinical factors such as a patient's cardiac history, laboratory and electrocardiogram findings, but also the risk status of a patient calculated using a validated risk score [1,2]. Despite this recommendation, variation in treatment practices seem to exist, with not every NST-ACS patient receiving care according to the guidelines. It has been suggested that the routine application of risk scores, in addition to clinical judgement, could improve the risk assessment process and could guide clinical-decision making [3-6]. However, it is unknown to what extent risk scores are used in practice and if they actually contribute to a cardiologist's decision. Although these risk scores, such as the GRACE [7] and the TIMI [8] risk score, have been extensively validated and are recommended in cardiac guidelines, a previous study concluded that physicians may have a sceptic attitude towards the use of risk scores in decision-making [9].

In this thesis we have studied the extent of guideline adherence in the management of NST-ACS patients with emphasis on the use of cardiac risk scores in clinical practice. Besides the actual use of risk scores in clinical practice, determinants for suboptimal cardiac risk score use were studied on a patient-, healthcare provider- and organizational-level. Furthermore, the impact of different components of clinical information, including risk score outcomes, on cardiologists' decision-making regarding performing coronary angiography was studied.

In **Chapter 2** a systematic review is presented regarding the extent of adherence of healthcare providers towards the European Society of Cardiology (ESC) and American College of Cardiology/American Heart Association (ACC/AHA) guidelines in the management of NST-ACS, and associated patient outcomes, and influential factors. It was found that lower guideline adherence was consistently associated with poorer prognosis, and that adherence varied widely between the reviewed studies. Adherence rates between 5.0% and 95.0% for acute and discharge pharmacological care, and between 16.0% and 95.8% for performing coronary angiography (CA) were found. Only a few studies looked into the use of different risk stratification methods, for which adherence rates were found varying between 34.3% and 93.0%. Several factors related to the patient and the organization were found that either increased or decreased guideline adherence.

In **Chapter 3** the design of a cross-sectional, multicentre, patient chart review regarding the extent of cardiac risk score use in Dutch hospitals is presented. In **Chapter 4** the findings of this study are reported. Data of 1788 patients discharged with a diagnosis of NST-ACS were analysed. Just as the results showed in Chapter 2, large variation in adherence rate was found.

A cardiac risk score was documented in 57.0% of the cases, and varied between thirteen hospitals from 16.7% to 87.0%. Results further showed that risk scores were more often used in obese patients and in former smokers. By contrast, risk scores were less often used in patients diagnosed with unstable angina, in patients who were resuscitated, in patients with in-hospital heart failure or in patients with tachycardia.

In **Chapter 5** the results of a semi-structured interview with healthcare providers regarding the use and implementation of risk scores are presented. In this qualitative study health care providers were asked for their motivation for cardiac risk score use (or not), and the associated benefits and risks that they experienced. They were also asked to describe the implementation process and facilitators and barriers that they perceived being of influence. It was found that healthcare providers disagree on the importance of cardiac risk scores in clinical decision-making. A clear distinction between intrinsic motivations and extrinsic motivations for change became clear. Healthcare providers who were intrinsically motivated to use risk scores experienced several benefits in processes of care. Healthcare providers who felt pressured by external parties to use risk scores in practice, were less likely to take account of the risk score in their treatment decisions. Furthermore, healthcare providers mentioned several factors that were determinative for successful adoption and implementation of cardiac risk scores. These were related to the risk score itself (e.g. clinical relevance, complexity of the score), to the healthcare provider (e.g. negative attitude, lack of motivation), and to the organization (e.g. lack of necessary resources).

To determine the actual importance of cardiac risk scores and other clinical information for cardiologists' decision-making, a clinical vignette study was conducted. Cardiologists were asked to decide upon performing coronary angiography or not in clinical cases of NST-ACS patients. In **Chapter 6** the development of a survey comprising a binary choice experiment with realistic descriptions of clinical cases (vignettes) is described. In the vignettes, clinical factors were systematically varied according to a fractional factorial design. To ensure accuracy, plausibility and clarity of the vignettes a panel of cardiologists was consulted for the selection of attributes and attribute levels.

In **Chapter 7** the results of the clinical vignette study are reported. It was found that cardiologists mainly base their decision-making for performing CA on three sources of clinical information, with elevated troponin levels and typical ischemic changes on the ECG making cardiologists more likely to perform CA, and severe renal dysfunction making cardiologists less likely to decide on CA. Factors for persistent complaints of chest pain, previous coronary artery disease, and presence of risk factors, hardly influenced cardiologists' decision-making. Risk score was highly associated with a patients' age, and therefore no firm conclusions could be drawn about separate effects of risk score or age on cardiologist's decisions. Looking at

the combined factor of age and risk score, it was found that cardiologists were more hesitant to perform CA in elderly patients with high risk according to a validated risk score, than in younger patients with intermediate risk.

To conclude, cardiac risk score use in practice is relatively low and varies widely between hospitals. We found several barriers that can possibly explain the large variation in adherence rates, mainly related to the healthcare provider and the organization. These major barriers comprised, among other things, the lack of a strong scientific evidence-base and clinical relevance (i.e. impact studies), type of motivation (i.e. intrinsic versus extrinsic), and lack of necessary resources in combination with complexity of the risk score (i.e. IT and management support). Furthermore, it was found that instead of multifactorial risk assessment, clinical decision-making was mainly driven by a limited number of clinical factors.

It is therefore recommended that:

- risk scores are used in addition to conventional risk assessment. In that way clinical judgement, i.e. implicit decision-making based on clinical experience and objective risk assessment by using a risk score can complement and enhance each other;
- future research focuses on the impact of risk score use on patient outcomes, as these results could accelerate the adoption and implementation of these scores in practice;
- when implementing these scores in practice, an implementation strategy, tailored to existing barriers in which intrinsic motivation is enhanced and necessary resources are provided, is recommended.

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Samenvatting

Voor een optimale behandeling van patiënten met een Non-ST-Elevatie Acuut Coronair Syndroom (NST-ACS) raden Europese (ESC) en Amerikaanse (ACC/AHA) richtlijnen aan dat artsen een risico-inschatting maken op basis van een zorgvuldige weging van meerdere factoren, waaronder de cardiale voorgeschiedenis, bloeduitslagen en elektrocardiogram bevindingen van een patiënt [1,2]. Tevens wordt aangeraden om gebruik te maken van gevalideerde klinische predictiemodellen, i.e. risico scores. Uit eerdere literatuur blijkt echter, dat ondanks deze aanbevelingen, variatie in de toewijzing van behandelingen bestaat. Niet iedere NST-ACS patiënt, gegeven zijn of haar risico status (laag, middel, hoog risico voor overlijden en/of herinfarct), ontvangt de zorg aanbevolen door de richtlijnen. Het routinematig gebruik van risico scores kan in de praktijk, als aanvulling op het klinisch redeneren van de arts, wellicht het risico-inschattingsproces verbeteren. De risico score kan fungeren als 'gids' in de besluitvorming [3-6]. Het is echter niet bekend in hoeverre risico scores worden gebruikt in de praktijk en of deze instrumenten ook daadwerkelijk bijdragen aan de besluitvorming van een arts. Hoewel deze risico scores, zoals de GRACE- [7] en de TIMI- [8] risico score, uitgebreid zijn gevalideerd en daarnaast in de richtlijnen als klasse 1 aanbeveling worden weergegeven, laat een eerder studie [9] zien dat artsen vaak een sceptische houding hebben tegenover het gebruik van risico scores in de praktijk.

In dit proefschrift hebben we de mate van richtlijnnaleving in de behandeling van patiënten met NST-ACS bestudeerd, met nadruk op het gebruik van risico scores in de praktijk. Daarnaast is gekeken naar mogelijke factoren die een rol spelen bij suboptimaal gebruik van risicoscores. Tevens is gekeken naar de waarde die cardiologen hechten aan verschillende soorten klinische informatie, waaronder de risico status van de patiënt volgens een gevalideerde risico score, in de besluitvoering rondom het wel of niet uitvoeren van een coronair angiografie.

In **Hoofdstuk 2** beschrijven we de uitkomsten van een systematische literatuurstudie naar de mate van richtlijnnaleving in patiënten met een NST-ACS. Ook kijken we naar de relatie tussen risicoscore gebruik, patiënten uitkomsten en factoren gerelateerd aan de patiënt, zorgverlener of de organisatie. Het blijkt dat in de studies waarin wordt gekeken naar de relatie tussen richtlijnnaleving en patiënten uitkomsten, lagere richtlijnnaleving significant geassocieerd is met een slechtere prognose in termen van overlijden/herinfarct. Tevens blijkt dat richtlijnnaleving tussen en binnen de verschillende studies aanzienlijk varieert. Percentages tussen de 5.0% en 95.0% zijn gevonden voor acute medicamenteuze behandeling en voor ontslagmedicatie, daarnaast zijn percentages tussen de 16.0% en 95.8% gevonden voor het uitvoeren van een coronair angiografie. In enkele studies is gekeken naar het gebruik van verschillende risico-stratificatie methoden, waarbij percentages werden gevonden die varieerden tussen de 34.3% en 93.0%. Daarnaast waren

verschillende patiënt- en organisatiefactoren geassocieerd met hogere of juist lagere richtlijnnaleving.

In **Hoofdstuk 3** geven we een beschrijving van het design van een cross-sectioneel, multicenter dossieronderzoek, waarbij medisch dossiers van patiënten zijn bekeken aangaande de mate van risico score gebruik. De resultaten zijn weergegeven in **Hoofdstuk 4**. Gegevens van 1788 patiënten, ontslagen uit 13 Nederlandse ziekenhuizen, met de diagnose NST-ACS zijn geanalyseerd. Net als in het systematisch literatuuronderzoek in hoofdstuk 2, is de variatie in risico score gebruik groot. In 57.0% van alle gevallen was een risico score (uitkomst) gedocumenteerd in het patiëntendossier, maar dit varieerde van 16.7% tot 87.0% tussen ziekenhuizen. De resultaten laten verder zien dat risico scores vaker worden gebruikt voor patiënten met obesitas of voor ex-rokers en minder vaak voor patiënten met instabiele angina pectoris, met hartfalen tijdens opname, met tachycardie of voor patiënten die zijn gereanimeerd bij binnenkomst in het ziekenhuis.

In **Hoofdstuk 5** beschrijven we de uitkomsten van semi-gestructureerde interviews met zorgverleners aangaande het gebruik en de implementatie van risico scores in de dagelijkse praktijk. In deze kwalitatieve studie is aan zorgverleners gevraagd naar hun motivatie voor risico score gebruik (of niet), naar ervaren voordelen en nadelen en is hen gevraagd het proces van implementatie te beschrijven met inachtneming van mogelijke bevorderende en belemmerende factoren. Het blijkt dat zorgverleners de waarde van risico scores voor klinische besluitvorming verschillend waarderen. Een duidelijk onderscheid is te maken tussen intrinsieke motivatie voor risico score gebruik en risico score gebruik als gevolg van externe druk. Zorgverleners die intrinsiek gemotiveerd waren, ervaarden verschillende voordelen, bijvoorbeeld in het opstellen van beleid en in de continuïteit van zorg. Zorgverleners, daarentegen, die het gevoel hadden dat het gebruik van risico scores is opgelegd, waren minder geneigd om voordelen te ervaren en de risico score daadwerkelijk te gebruiken in de besluitvorming. Afgezien van het type motivatie, beschreven zorgverleners verschillende factoren die de mate van risico score gebruik beïnvloeden en bepalend zijn voor een succesvolle adoptie en implementatie van de scores. Deze factoren waren gerelateerd aan de score zelf (complexiteit en klinische relevantie van de score), de zorgverlener (houding tegenover de score) en de organisatie (tekort aan benodigde hulpmiddelen of steun van het management).

Om het daadwerkelijke belang van risico scores en andere klinische informatie voor de besluitvorming van een arts te bepalen, is een klinische vignetten studie opgezet en uitgevoerd. Cardiologen werd gevraagd een beslissing te nemen rondom de uitvoer van een coronair angiografie in verschillende scenario's van een patiënt met NST-ACS. In **Hoofdstuk 6** wordt de ontwikkeling van een kwantitatieve survey, bestaande uit binaire keuze experimenten

waarbij gebruik is gemaakt van realistische omschrijvingen van patiënt scenario's (vignet), in detail beschreven. De vignetten zijn opgebouwd uit verschillende factoren (aanwezigheid van risicofactoren) en niveaus (geen, één, twee of meer), welke systematisch zijn gevarieerd middels een fractioneel factorieel design. Daarnaast is gebruik gemaakt van een panel van cardiologen, die de vignetten hebben beoordeeld op de volgende punten: accuraatheid, realiteit en duidelijkheid.

In **Hoofdstuk 7** beschrijven we de resultaten van de klinische vignetten studie. Het blijkt dat besluitvorming van cardiologen aangaande het wel of niet uitvoeren van een coronair angiografie met name gebaseerd is op drie klinische factoren. De aanwezigheid van verhoogde cardiale markers in het bloed (troponine) en typische afwijkingen op het elektrocardiogram maken dat cardiologen eerder geneigd zijn te kiezen voor de uitvoer van een coronair angiografie, daarentegen maakt ernstige nierinsufficiëntie cardiologen terughoudend bij het uitvoeren van een coronair angiografie. Factoren zoals persistente klachten van pijn op de borst, bekend met coronair vaatlijden en de aanwezigheid van risicofactoren voor hart- en vaatziekten waren nauwelijks van invloed op de besluitvorming. Risico score was sterk geassocieerd met de leeftijd van de patiënt, waardoor het niet mogelijk was om harde uitspraken te doen over het effect van elk van deze twee factoren afzonderlijk op de besluitvorming van cardiologen. Kijkend naar de gecombineerde factor van risico score en leeftijd, blijkt dat cardiologen terughoudender zijn in het uitvoeren van een coronair angiografie in oudere patiënten met een hoog risico volgens een gevalideerde risico score, dan in jongere patiënten met gemiddeld risico.

Concluderend kunnen we zeggen dat risico score gebruik in de dagelijkse klinische praktijk relatief laag is en sterk varieert tussen ziekenhuizen. Verschillende belemmerende factoren zijn gevonden die deze variatie mogelijk verklaren, welke met name zijn gerelateerd aan de zorgverlener en de organisatie. Deze barrières betreffen, onder andere, een marginale wetenschappelijke onderbouwing van het effect van de risico score en/of de klinische relevantie in termen van gereduceerd risico op overlijden van de patiënt bij risico score gebruik (i.e. tekort aan impact studies). Daarnaast blijkt dat de motivatie (i.e. intrinsiek versus extrinsiek) van de zorgverlener bepalend is voor risico score gebruik en dat een tekort aan benodigde hulpmiddelen – met name ICT of management ondersteuning – de implementatie van de scores in de praktijk verder bemoeilijkt. Verder blijkt dat besluitvorming van cardiologen met name gebaseerd is op enkele belangrijke klinische factoren, in plaats van een weging van meerdere factoren, zoals geadviseerd door de richtlijnen.
Wij bevelen daarom aan dat:

- Risico scores worden gebruikt in aanvulling op het klinisch oordeel van de arts. Op die wijze kan impliciete risico-inschatting en besluitvorming gebaseerd op de klinische blik van een arts en objectieve risico-inschatting en besluitvorming door het gebruik

van een gevalideerde risico score elkaar aanvullen en versterken;

- Toekomstig onderzoek zich richt op de impact van risico scores in termen van patiënten uitkomsten, aangezien deze resultaten de adoptie en implementatie van de scores in de praktijk kan versnellen;
- De scores worden geïmplementeerd door gebruik te maken van een implementatie strategie aangepast aan aanwezige barrières, waarin intrinsieke motivatie van zorgverleners wordt aangesproken en de benodigde hulpmiddelen zijn gegarandeerd.

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Curriculum vitae

Josien Engel was born on April 14th 1986 in Gouda. Soon after she moved to Wageningen, where she grew up. In 2003 she started nursing school at the University of Applied Sciences in Nijmegen (HAN). During her trainee as a nurse, she studied abroad in Copenhagen (Denmark), where she worked at Hvidovre Hospital on the emergency department. She gained her bachelor in nursing in 2007, and started her nursing career at the Radboud University Medical Center in Nijmegen, where she worked at several departments. In 2008 she started her masters in Nursing Science at the University of Utrecht. For her master thesis she studied, in a before-after study, the effect of a tailored multifaceted implementation strategy in the implementation of an evidence based nutritional guideline for stroke patients under supervision of Dr. Thóra Hafsteindóttir and Dr. Roland van Linge. During that same period, she worked as a registered nurse on the neurology department of the Radboud University Medical Center. In 2011 she started as a PhD candidate at the EMGO+ Institute for Health and Care Research / VU University Medical Center. She was a member of the research group safety4patients and her PhD project was part of the large Dutch Patient Safety study (*Monitor Zorggerelateerde Schade*). Since January 2015 she is working as a lecturer in nursing at the HU University of Applied Sciences in Utrecht, and as a lecturer of the summerschool and online course 'Clinical Leadership in Healthcare' of the University of Utrecht.