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Measuring quality of care in the treatment of acute coronary syndrome

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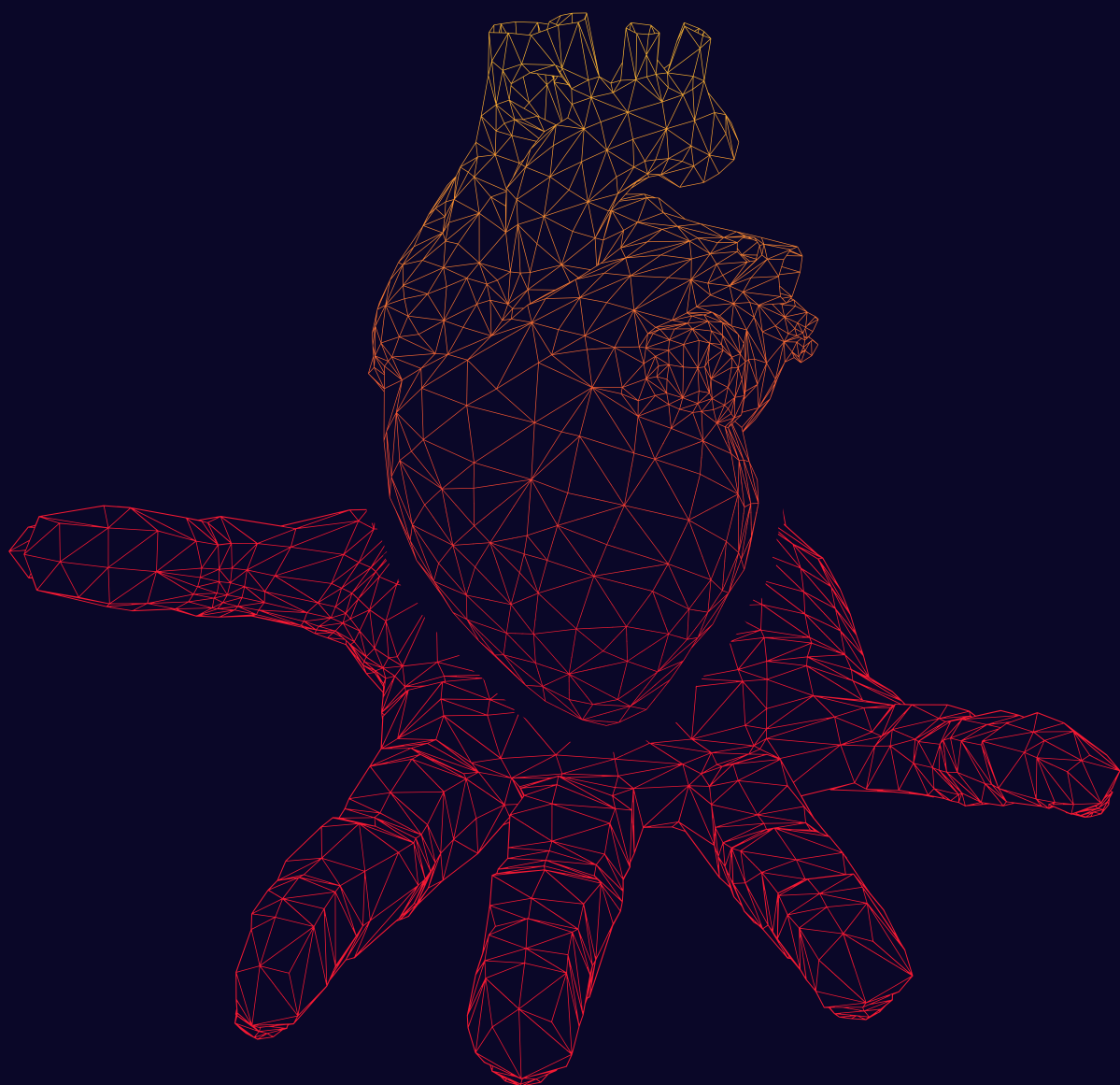
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Measuring Quality of Care in the treatment of Acute Coronary Syndrome

DANIËLLE C. EINDHOVEN



**Measuring Quality of Care
in the treatment of
Acute Coronary Syndrome**

Daniëlle Catharina Eindhoven

The studies described in this thesis were performed at the department of Cardiology of the Leiden University Medical Center, Leiden, The Netherlands.

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Measuring Quality of Care in the treatment of Acute Coronary Syndrome

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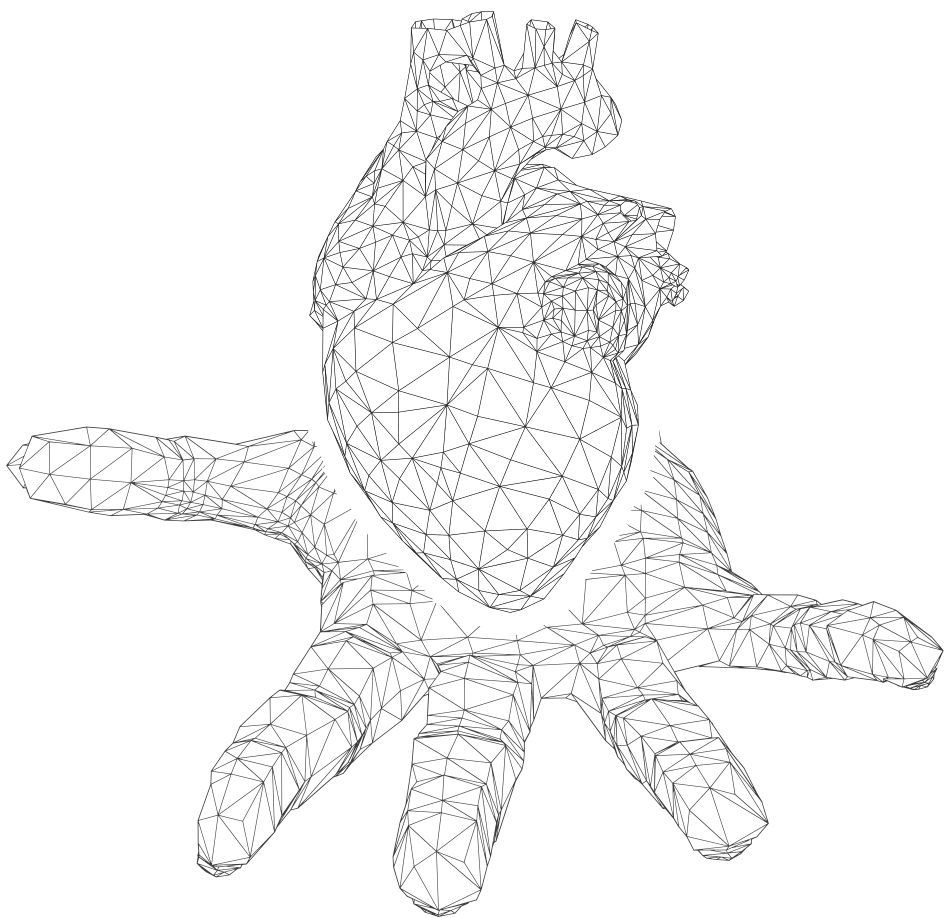
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Voor mijn ouders

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Chapter 1

General introduction

Based on the paper entitled *The year of Transparency: Measuring Quality of Cardiac Care.*

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INTRODUCTION

Medicine changed dramatically during the last decades with the introduction of multiple life-saving solutions and diseases now becoming treatable which were deemed untreatable in the past. In the beginning of 20th century, an acute coronary syndrome was treated with bed rest and 'expectant treatment', as far away for the nurses' station, so that they would not be disturbed by the frequent telephone ringing.¹ In 1975 the treatment evolved to achieve rapid myocardial reperfusion by streptokinase, cardiac surgery or percutaneous coronary intervention.¹ However, many of these new treatment modalities are more complex and request an excellent organisation, which has not always evolved equally.

Meanwhile, many treatments are initiated without a solid risk assessment and thorough clinical evaluation and may even cause harm to the patients. A study in the U.S. suggests that medical errors are the third leading cause of death emphasizing that patient safety is a serious health care issue.² Since the To Err is Human report in 1999, different reports raised an increased attention for quality of care and safety.^{3,4} After preclinical research (in vitro and in vivo), clinical research (randomised controlled or large observational trials), this thesis focusses on the next phase: retrospective quality of care studies and whether all research and guidelines do work in real clinical practice.

What is quality of care?

'Primum Non Nocere', or 'First, Do No Harm', is the well-known sentence from the Oath of Hippocrates, which doctors swear at the start of their career.⁵ These ethical standards are still considered to be a main priority in health care and form the basis of quality of health care. The second layer which defines 'what is good care' are the professional standards or guidelines of the Royal Dutch Medical Association (Koninklijke Nederlandsche Maatschappij tot bevordering der Geneeskunst, KNMG) or the Scientific Societies (Wetenschappelijke Verenigingen). This is anchored in laws concerning health care, like the Individual Health Care Professions Act (Beroepen in de Individuele Gezondheidszorg, BIG) and Medical Treatment Act (Wet op de Geneeskundige Behandelingsovereenkomst, WGBO), which are known to be the third layer. The measurement of quality indicators is the fourth and final layer and the modern way of defining good quality of care. The measurement of quality of the care, both on a local and national level, is the focus of this thesis.

Quality of care has various definitions. The National Academy of Medicine, formerly called the American Institute of Medicine defined quality of care as *'the degree to which health service for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge'*.⁶ In 2003, quality of care has been defined by the Agency for Healthcare Research and Quality of the United States as *doing*

*the right thing, at the right time, in the right way, for the right person—and having the best possible results.*⁷ In The Netherlands, the definitions on quality of care were translated into six aspects; Safety, Effective, Patient centered, Timely, Efficient and Equitable.⁸

PART ONE – QUALITY OF CARE ON A LOCAL LEVEL

Patient Safety

Patient safety is defined as the prevention of harm to patients and forms the cornerstone of high quality of care. Measuring patient safety at a local level constitutes the focus of the **first part of this thesis**. In 1999, the National Academy of Medicine, published a report called '*To Err is Human*', which drew attention to the fact that a significant number of patients suffered from injuries or even had died as a result of care delivered in hospitals.⁴ Subsequently, various studies in different countries reported that 2.9–16.6% of in-hospital patients experienced one or more adverse events and that in 5–13% of the adverse events the patients died.^{9–19} A recent report by Makary et al. showed that adverse events are still the third leading cause of death in the United States.² This formed the basis of an increased focus on the assessment and management of patient safety.

The conceptual framework of patient safety is based on the causal chain of Donabedian (differentiating between structure, process and outcome) and Reason's Swiss cheese model (differentiating between latent errors on an organisation level and active errors of human interaction).^{20,21} (**Figure 1**) In the assessment of events, a difference is made between (unintended) events during the process of care (i.e. incidents or errors) and in the (unintended) outcome of events (i.e. complications or adverse event). Furthermore, a causal relationship was assessed between the process and outcome. As an example, if someone who should have been vaccinated against influenza contracts the prevalent strain of the disease, it is quite possible that this could have been prevented. On the other hand, the reoccurrence of acute coronary syndrome in an individual patient might not have been prevented by b-blockers, even if at a population level the benefits are clear.²² A detailed description of the used definitions is noted in **Box 1**.



Figure 1: Structure, process and outcome indicators, including latent and active errors.

After finding a substantial number of preventable deaths, the project of EMGO+/NIVEL called '*Zorggerelateerde Schade*' (literally Health Care related Injuries) in 2004, 2008 and 2012, raised the attention on Patient Safety Management in Dutch hospitals. As a

result, a national safety program for hospitals '*Voorkom schade, werk veilig*', started in 2007.²³ This was based on nationwide research on adverse events by EMGO+/NIVEL, in which retrospective patient records review and database algorithms were assessed. The report raised awareness significantly in The Netherlands with respect to patient safety.²⁴ However, due the general hospital-wide approach, this report provided hardly any insight into causal relations on a departmental level. The development of specific interventions

Box 1: Definitions in the field of patient safety.

Adverse event is (1) an unintended injury (physical and/or mental) which results in (2) temporary or permanent disability, death or prolonged hospital stay and (3) that is caused by health care management rather than by the patient's underlying cardiac disease.

Calculated Risk is a balanced risk or calculated side effect of a treatment described in literature, in which the intended effect of the treatment is considered of greater importance than the severity of the injury or the chance of an injury.

Causation refers to injury caused by health care management including acts of omission (inactions) i.e. failure to diagnose or treat, and acts of commission (affirmative actions) i.e. incorrect diagnosis or treatment, or poor performance.

Complaint is any objection raised to the action or functioning of a health care provider, coming from the user of the health care which is provided.

Complication is any unintended and undesired injury during or after receiving health care, which requires treatment or leads to temporary or permanent injury.

Disability refers to temporary or permanent impairment of physical or mental function attributable to the adverse event (including prolonged or strengthened treatment, prolonged hospital stay, readmission, subsequent hospitalisation, extra outpatient department consultations or death).

Error is failure of performing a planned activity (failure of performance) or a wrong plan to achieve its intended outcome (failure of planning).

Health care management includes the action of individual hospital staff as well as the broader systems and care processes. Health care management is any care related activity that involves the delivery of care or monitoring of health which is provided by individuals or a team of professionals.

Incident is any unintended or unexpected event which could have or did lead to harm for one or more patients receiving health care.

Near Miss is a unintentional event that (1) does not cause harm to the patient because their consequences are recognized and corrected on time, or (2) whose effects do not affect the physical, psychological or social functioning of the patient.

Preventable adverse event is an adverse event resulting from an error in management due to failure to follow accepted practice at an individual or system level. Accepted practice was taken to be 'the current level of expected performance for the average practitioner or system that manages the condition in question'.

Process deviation was defined as every operation or treatment that differentiated from the MISSION! Protocol, such as additional procedures (a pacemaker implantation or second PCI), prescription of extra medication other than described in the protocol (use of antiarrhythmics, anticoagulation, inotropics or diuretics) or omission of a procedure (no diagnostics performed).

Unintended injury refers to any disadvantage for the patient that leads to prolonged or strengthened treatment, temporary or permanent (physical and/or mental) impairment or death.

Based on Wagner⁶⁶ and Langelaan^{67, 68}.

at each department in order to improve patient safety appeared even more challenging, particularly in cardiology, being a department with a high intervention rate and a large number of patients with life-threatening illnesses. High-risk industries, such as the aviation and chemical industry, are required to perform structured assessments of all processes contributing to a particular activity, which allows them to make a reasoned claim regarding safety. Inspired by high-risk industries and best-practice hospitals, the aim of the **first part of this thesis** is to provide a methodology to review patient safety on a local level and to define if our *work process is sufficiently safe*.²⁵

The **second chapter** analyses process deviations and the correlation with adverse events in hospitalised patients who are treated for an acute coronary syndrome according to the protocolised care pathway, called MISSION!, in the Leiden University Medical Center. The definition of an acute coronary syndrome and the description of the MISSION! Protocol is explained in **Box 2**. The **third chapter** describes the results of a retrospective patient record review study concerning incidence, type, nature, and preventability of AEs among hospitalised acute coronary syndrome-patients in The Netherlands. The **fourth chapter** focusses on the treatment of female and their higher risk on adverse events.

Box 2: Acute myocardial infarction and the MISSION! Protocol.

Acute coronary syndrome

Acute coronary syndrome is a high-risk manifestation of coronary artery disease, ranging from unstable angina pectoris, non-ST-segment elevated myocardial infarction (NSTEMI) to ST-segment elevated myocardial infarction (STEMI). Although rupture or erosion of a vulnerable atherosclerotic plaque frequently leads solely to progression of plaque volume, due to an unfortunate turn of event it might give rise to a cascade of inflammation, thrombus formation and partial or complete occlusion of the coronary artery resulting in acute ischemia or necrosis of the myocardium. A patient with a NSTEMI or STEMI shows elevated level of cardiac biomarkers (Creatine-kinase or Troponine) due to ischemia.

MISSION!

The MISSION!-protocol contains a prehospital, in-hospital, and outpatient framework for clinical decision making and treatment for the different diagnosis in acute coronary syndrome (STEMI, NSTEMI, UAP or another diagnosis like and old ambulatory infarction). This study is focussed on the in-hospital program (early reperfusion, same diagnostic trajectory like 2D-echocardiography, structured medical therapy, and disease education). Generally, patients are planned for discharge 12 hours after a coronary angiography, or 48 hours after a percutaneous coronary intervention. The MISSION!-protocol is based on the evolving guidelines of the European Society of Cardiology.^{63,64,65}

PART TWO – QUALITY OF CARE ON A NATIONAL LEVEL

The different perspectives in the assessment of Quality of Care.

After the assessment of patient safety on a local level, the second part focusses on quality of care on a national level. The quality of care assessment or indicators are used to assess the quality of care and to compare hospitals or caregivers. The assessment of quality of care is becoming increasingly important in healthcare, both globally and in The Netherlands. With the transition into a regulated healthcare market system in 2006, insurance companies received a central role and the shared legal responsibility for the quality of cost-effective care.²⁶ This responsibility created the legal need to develop a system in which quality of care can be measured and monitored.²⁷ Currently, hospital accreditation is already based on quality measurements and in the future, reimbursement will most likely also be based on quality instead of price and volume only.²⁸ The Dutch Minister of Health had declared the year 2015 to be the year of transparency, thereby stressing the need to improve the reporting of quality of care.²⁹ With the increasing importance of transparency, knowledge on quality measurements will become vital in daily clinical cardiac care.

The aim of measuring quality of care differs depending on the different stakeholders involved in the healthcare system.³⁰ Patients aim for the best possible clinical outcome, patient-cared-care approach and need quality measurements to be able to take informed decisions. Healthcare professionals aim for the best possible outcome for a maximum number of patients and, additionally, need quality measurements to benchmark results with other healthcare professionals in order to identify improvement opportunities. Healthcare insurance companies aim for the best possible (long-term) value for the money spent on behalf of their customers (insured patients). The government aims to achieve the best possible public health at a stated budget, while guaranteeing financial and physical accessibility and affordability for all inhabitants.³¹ (Figure 2)

How to assess Quality of Care?

The previously mentioned causal chain of Donabedian, is also used in the assessment of measurable indicators for quality of care: structure, process and outcome indicators.²¹ (Table 1)

Structure indicators reflect the system and setting in which care is delivered and relate directly or indirectly to staff expertise, the organisation logistics or capacity. For cardiac care, examples are PCI volume, availability of a catheterization laboratory and the educational level of the nursing staff. Structure indicators are less likely to be influenced by medical professionals and therefore less useful to monitor programs for quality improvement. They reflect the average results for a large group of providers, not for individual providers. The

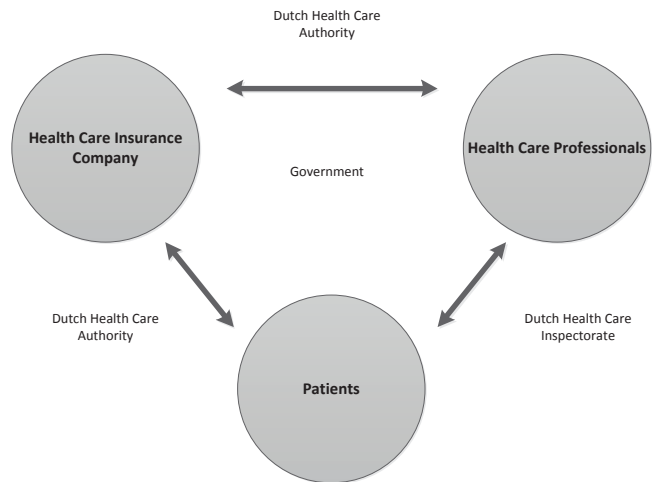


Figure 2: Different positions in the health care system in the Netherlands

Table 1

	Structure Indicators	Process Indicators	Outcome Indicators
Example	PCI-volume a year Availability of cathlab Education level of the nurses	Medical prescription according to guidelines Door-to-balloon-times	Morbidity and mortality rates Functional health status Patient Satisfaction Costs
Advantages	Appropriate. If associated with outcome, inexpensive proxies of cardiovascular outcomes.	Reflect care that patients actually receive. Actionable from provider perspective. Clear link to quality improvement activities.	The ‘bottom-line’ of cardiology Outcomes measurement alone may improve outcomes.
Disadvantages	Most variables not actionable from provider perspective. Imperfect proxies for outcomes reflect average results for large groups of providers, not individuals.	Little information about which processes are important for specific procedures.	Numbers too small to measure with adequate procedure-specific outcomes for most hospitals and procedures. Outcomes measures that are not procedure-specific less useful for purposes of quality improvement.

Based on Birkmeyer et al. which is applied on examples in the field of Cardiology.

advantage of these structure indicators is that they are expedient and relatively inexpensive to collect and can be used in plain hospital comparisons. Structure indicators are in general of limited use in clinical practice although a large study ($n = 457,498$) was published in which a relationship was found between increased operator/institutional volume of PCI procedures and a decrease in adverse outcomes and costs of hospitalisation.³² However, other studies demonstrated that an increase of volume above a certain threshold is not

related to improved outcomes. Hence, some of these structure indicators may be useful to define minimal requirements.

Process indicators describe the care patients actually receive. Examples for cardiac care are door-to-balloon-times in patients with a ST-segment elevation myocardial infarction and medication prescription according to the guidelines.^{33, 34} The usefulness of process indicators and the association with clinical outcome measures has been thoroughly established. In patients with an acute myocardial infarction, Peterson et al. showed a correlation between processes of care and outcome. With every 10% increase in process adherence (for example medication use according to clinical guidelines) there was an associated 10% decrease in in-hospital mortality.³³ Another study demonstrated that 6% of hospital-level variation of 30-day mortality rate could be explained by the performance on process measures.³⁵ In heart failure, the relationship between process and outcome is however modest. In the OPTIMIZE-HF study, none of the process measurements were associated with a decrease in 60- or 90-day mortality.³⁶ In case of a proven association, process indicators can be useful to monitor if aspects of clinical practice are likely to result in an improvement of the quality of care. A limitation, however, is that there is a lack of evidence on which processes are important for specific procedures. Importantly, although the use of process indicators is known to be effective in general, they are not able to mark the quality of care provided to individual patients since it can be necessary to deviate from the normal care process in order to provide optimal care for that specific patient. For example, prescribing beta blockers after an acute myocardial infarction is considered common practice. However, patients with symptomatic bradycardia after an acute myocardial infarction should not receive a beta-blocker, thereby stressing the need for a connection with clinical data, which are more time-consuming to require.

Quality of care is most effectively measured by clinical outcome measures, referring to the effect of the provided care on the health status of patients. These outcome measures can be translated to *outcome indicators*. Examples of these are overall mortality rate, hospital readmission rate, functional health status and patient satisfaction. Outcome measurement is considered the most important measurement of quality of care but has to be acquired per patient and is therefore relatively time-consuming and expensive. In 2013, the Court of Audit (Algemene Rekenkamer) concluded that the quality of most indicator sets is limited and that only 7 % of the indicators collected by hospitals were outcome indicators.³⁷

The relationship between registration of quality indicators and patient outcomes

Since registration is a time-consuming process, it is important to ascertain whether the used quality indicators actually provide the desired effect of improving quality of care.

Chatterjee et al. have described three mechanisms by which registrations can help to improve patient outcomes.³⁸

First of all, *reporting about quality of care among cardiology departments itself* can lead to more awareness and an incentive for hospital leaders and clinicians to improve the care that is provided. In order to achieve this, it is important that results can be shared safely. Studies show that departments that pay explicit attention to quality of care, show improved outcomes in care. This is called the Hawthorne effect.³⁹

Public reporting can also be a powerful incentive for clinicians and hospital leaders to improve. In addition, public reporting provides transparency in quality of care and can thereby increase the confidence of patients in the healthcare system. However, public reporting of quality indicators in the United States also demonstrated some disadvantages. First of all, states that publicly report on quality of care did not show differences in outcome compared to states that did not report.⁴⁰ A further concern of public reporting is that it will lead to risk aversion among physicians, deferring patients with more complex pathology, as is demonstrated in the literature. For example, in the United States, the majority (89 %) of interventional cardiologists have reported that the decision to intervene in critically ill patients was influenced by the fact whether or not they participated in the reporting of quality measures.⁴⁰ A registry confirmed this trend in practice, showing that patients in reporting states (e.g. New York) were less likely to undergo a PCI procedure if they were in shock.⁴¹ Public reporting of CABG mortality in New York led to an increase of sicker patients being referred to the adjacent state Ohio.⁴² Although transparency in quality indicators is increasing in The Netherlands, the results are currently not linked to individual caregivers. The Society for Cardiothoracic Surgery in Great Britain and Ireland, in collaboration with the National Health Service, provide open access information on treatment results of all individual cardiothoracic surgeons.⁴³ In The Netherlands, the aim of the Dutch government is to publish results of quality of care measurements at a national website for patients in order to improve transparency and to help patients in making informed decisions (www.kiesbeter.nl).

Pay-for-performance is the newest quality improvement mechanism, which is gaining attention from healthcare leaders and healthcare insurance companies as a strategy for maximizing quality while controlling costs. Pay-for-performance implies a shift in paying for quality healthcare instead of volume of care, which can be a strong stimulus to improve quality.^{38, 44}

Registration of quality of care in The Netherlands.

National quality measurement

National quality measurements are initiatives from government, supervision institutions, insurance companies and patient organisations. From the perspective of the individual hospital and/or cardiology department these initiatives can be interpreted as external requests for accountability. The Dutch Healthcare Inspectorate (*Inspectie voor de Gezondheidszorg en Jeugd, IGJ*) has an important task, as described in Article 36 of the Healthcare Insurance Act, to verify if hospitals meet the minimum level of quality according to general healthcare acts and the professional standards as defined by the professional organization of the different medical specialists.²⁶ Verification of the data is achieved by surveillance of compliance to the law, regulations, professional standards and guidelines. The Dutch Healthcare Inspectorate focuses on surveillance of the highest risks by mostly collecting process and structure indicators. For ST-segment elevation myocardial infarction, outcome, structure and process indicators (number of PCI procedures, in-hospital or 30-day mortality, door-to-needle time or door-to-balloon time and the percentage of patients referred for cardiac rehabilitation) are acquired. For pacemaker and implantable cardioverter defibrillator implantations the number of procedure-related complications within 90 days has to be registered.⁴⁵

Hospitals use external accreditation programs to prove and objectify a certain level of quality of care as well as maintenance of quality of care to outsiders. The Q-Mentum, formerly known as The Netherlands Institute for Accreditation in Healthcare (*Nederlands Instituut voor Accreditatie in de Zorg, NIAZ*) or Joint Commission International aim to assure and improve Dutch healthcare by using an international accreditation program. Besides quantitative quality indicators, the accreditation systems comprise explicit quality policies and quality instruments, such as incident reporting and audits.

To reduce rising health care costs while improving quality of care, the Dutch healthcare system has changed in 2006 towards a regulated health care market. In order to achieve this, two important acts were introduced: the Healthcare Insurance Act (*Zorgverzekeringswet*) and the Act of Regulation of Healthcare (*Wet Marktordening Gezondheidszorg*).^{26, 46} In the new system the health insurance companies play a central role, positioned between patients and caregivers, with a shared responsibility to ensure good quality and cost-effective care. For the first time it became possible for the insurance companies to selectively contract care based on the quality of the provided care. Additional to the responsibility in limiting the rising healthcare costs, insurance companies are required to analyse and interpret quality of care provided by caregivers. Article 14 of the Healthcare Insurance Act, and the general directorial derived from this act, states that insurance companies share

the responsibility for efficient and timely healthcare of good quality, based on professional standards defined by the scientific professional organisations and healthcare providers. The explanatory memorandum of the act states that more information on outcome of caregivers will be available in the future.⁴⁷ Currently, however, more attention is given to the volume and cost agreement than to the provided quality of care.^{48,49} The Dutch Healthcare Authority (*Nederlandse Zorgautoriteit, NZa*), who has the task of overseeing the regulated healthcare market, is positive about the increased attention to quality of care in contracting during recent years.⁵⁰ A report of the Council for Public Health and Healthcare (*Raad voor de Volksgezondheid en Zorg, RVZ*) concluded that health insurance companies have to be more transparent about the criteria used for contracting care, which caregivers are contracted and how patients were involved in the process of contracting care.⁵¹

Quality Indicators used in a cardiology department.

In The Netherlands, the quality of cardiac care is measured by different stakeholders and the different quality indicators are provided by the cardiology departments or on a hospital level. In July 2017, The Netherlands Heart Registration (*Nederlandse Hart Registratie, NHR*) is founded, which is a fusion between three Dutch registries in cardiology and cardiothoracic surgery: 1) National Cardiovascular Data Registry (NCDR), 2) the Supervisory Committee for Heart Interventions in The Netherlands (*Begeleidingscommissie Hartinterventies Nederland, BHN*) and 3) *Meetbaar Beter*. Recently, examples from clinical practice show the downside of too many quality indicators. Registration of clinical parameters are known to be a laborious and time-consuming task, resulting in less time for actual patient care.⁵²⁻⁵⁴ Fraud with quality indicators is seen when hospitals struggle to meet the quality criteria or to measure the quality indicators.⁵⁵ In The Netherlands, around 3,500 indicators for quality assessments in general hospitals exist. The majority, around 96%, is requested by the insurance companies and patient representatives. The remaining 4% is requested by the Dutch Health Care Inspectorate, which composes around 3,500 variables and resulted in 250 indicators in 2017.⁵⁶ The QUASER study, in which the development of quality improvement of the different health care systems in European hospitals was compared, showed an excessive amount of indicators and external audits in The Netherlands.⁵⁷ Moreover, the indicators in the six countries were comparable, but not similar due to the use of different definitions for the numerators and denominators.

Criteria for a good Quality Indicator

As addressed before, the results of any measurement must be relevant for the different stakeholders in healthcare. For the use and development of quality indicators it is also important to take into account that indicators are scientifically acceptable. This means the indicators should be reliable and valid.⁵⁸ *Reliable* means that the indicator provides the same result on repeated measures and that the dataset is as complete as possible with

uniform datasets which are collected in a uniform way. Also, the Dutch Federation of University Medical Centres (Nederlandse Federatie van Universitair Medische Centra, NFU) points out in their report the importance of a central vision on registration of care and the value of a uniform standardised dataset. They aim to develop a uniform structure of elementary data elements and the use of a unified medical language based on international standards.⁵⁹ The use of universal definitions is encouraged by the International Consortium for Health Outcomes Measurement (ICHOM), an international non-profit organisation with the aim of transforming healthcare systems by measuring and reporting patient outcome.⁶⁰

Validity means that the indicator measures what it is intended to measure. This requires a good methodological quality, taking into account potential differences in casemix and random variation. A common remark heard by healthcare providers is that they are concerned about the lack of a proper case-mix correction and that a negative outcome compared with others can be explained by the increased complexity of their patient population compared to other hospitals. A good casemix correction applied in crude data could change the compared clinical outcome and is important to avoid unintended consequences.^{42, 61, 62} Furthermore, it is important to remember that quality indicators are merely a proxy of the actual quality of care. Therefore, the indicators should give appropriate coverage of the quality of care of a department and be in line with the crucial aspects of current strategies to improve quality of care.

Claims data

With the growing importance of quality assessment and the search for efficient data collection, routinely collected claims data are being used more frequently and studied for cardiac outcome measurements. Benefits of the claims data are the automatic and continuous data acquisition which makes it less laborious for health care professional to gather care outcome measurements. Claims data have the advantage to cover nationwide, do not depend on hospital participation and are useful for chain of care evaluation (including connection with external datasets). However, claims data are collected for billing purposes rather than for research. **Chapter 5** shows the validation of claims data in the assessment of medical treatment in the first year following acute coronary syndrome. **Chapter 6** uses the claims data to clarify if there are differences in medication use during one year following acute coronary syndrome, stratified for type of infarct, age and gender. In **chapter 7**, claims data is used to analyse the 'Weekend-effect' in patients with an acute myocardial infarction. Previously, several studies have shown that patients admitted with an acute myocardial infarction during the weekends have a higher mortality rate than those admitted during weekdays, possibly attributable to less trained personnel available and a lower use of medical procedures.⁵⁻¹⁰ **Chapter 8** concludes with the potential conflict

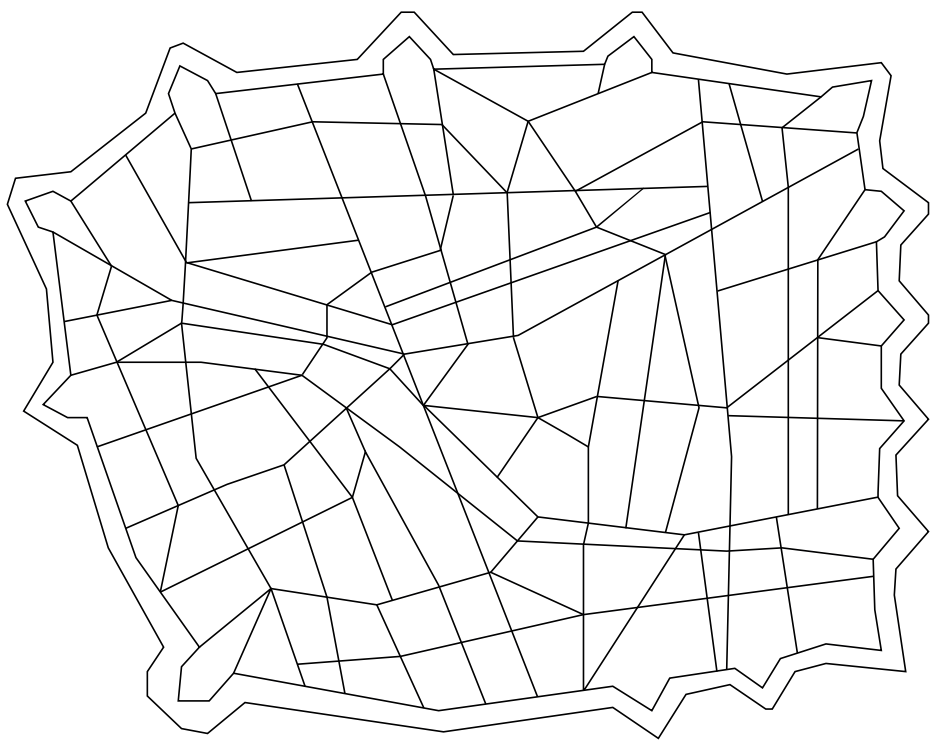
between patient privacy and the collection of patient data in quality-of-care registries and the impact of the new European law, the General Data Protection Regulation.

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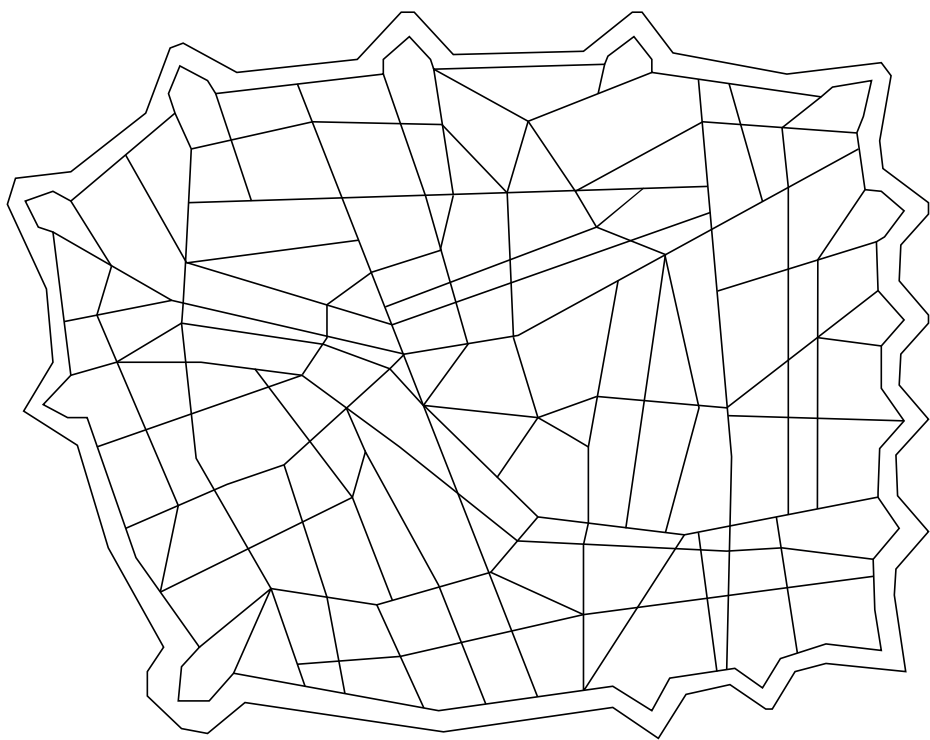
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Part One

Quality of Care on a Local Level



Chapter 2

Design and reliability of a specific instrument to evaluate patient safety for acute myocardial infarction patients treated in a pre-defined care track: a retrospective patient record review study in a single tertiary hospital in the Netherlands.

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ABSTRACT

OBJECTIVE: Numerous studies have shown that a substantial number of patients suffer from adverse events (AE) as a result of hospital care. However, specific data on adverse events in acute cardiac care are scarce. The current manuscript describes the development and validation of a specific instrument to evaluate patient safety of a predefined care track for acute myocardial infarction (AMI) patients.

SETTING AND PARTICIPANTS: A total of 879 hospital admissions treated in a tertiary care center for an acute myocardial infarction (age 64 ± 12 years, 71% male).

MAIN OUTCOME MEASURE: In the first phase, the medical records of AMI patients warranting coronary angiography or coronary intervention were analysed for process deviations. In the second phase, the medical records of these patients were checked for any harm that had occurred which was caused by the health care provider or the health care organisation (adverse event) and whether the harm that occurred was preventable.

RESULTS: Of all 879 patients included in the analysis, 40% ($n = 354$) had one or more process deviation. Of these 354 patients, 116 patients (33%) had an adverse event. AE-patients experienced more process deviations compared to non-AE-patients (2 ± 1.7 versus 1.5 ± 0.9 process deviations per patient, $p = 0.005$). Inter-rater reliability in assessing a causal relation of health care with the origin of an adverse event showed a kappa of 0.67 (95% CI 0.51 – 0.83).

CONCLUSION: This study shows that it is possible to develop a reliable method, which can objectively assess process deviations and the occurrence of AEs in a specified population. This method could be a starting point for developing an electronic tracking system for continuous monitoring in strictly pre-defined care tracks.

INTRODUCTION

Patient safety, defined by the National Academy of Medicine, formerly called the American Institute of Medicine, as the prevention of harm to patients, is the minimum prerequisite for a good quality of care.¹ In 1999 they published a report called 'To Err is Human', which drew attention to the fact that a significant number of patients suffered from injuries or even had died as a result of care delivered in hospitals.² Subsequently, various studies in different countries reported that 2.9% to 16.6% of in-hospital patients experienced one or more adverse events and that in 5% to 13% of the adverse events the patients died.³⁻¹³ In these studies, an adverse event (AE) was defined as an unintended injury that results in disability at the time of discharge, death, or prolonged hospital stay and is caused by health care management rather than by the patient's underlying disease process.

In various studies, a large variation in the incidence of adverse events among the different hospital departments was shown (0.5%-29.9%).^{4 14-16} However, these studies had a general hospital-wide approach and provided hardly any insight in causal relations on a departmental level. To develop specific interventions at each department in order to improve patient safety appeared even more challenging. Particularly cardiology, which is a department with a high intervention rate and a large number of patients with a life threatening illnesses. A subset of studies contain results on the occurrence of AE among general cardiac patients, based on small numbers of patients and showing a substantial variety in the incidence of AE (13.3%-29.9%).^{15 16} Therefore, sufficiently powered studies are needed for specific patient groups to gain more insight into the incidence of (preventable) AEs and to define '*How safe is our care*'.

Inspired by high-risk industries and best-practice hospitals, the aim of this study is to provide a system to review our work and to define if our work process is sufficiently safe. High-risk industries, such as the aviation and chemical industry, are required to perform structured assessments of all processes that contribute to a particular activity, which allows them to make a reasoned claim regarding safety. In the healthcare sector, best-practice hospitals such as the Intermountain Healthcare group, provide a framework like the Quality and Patient Safety Plan upon which an integrated and comprehensive program to monitor, assess and improve the quality and safety of patient care delivered.¹⁷ This study attempts to analyse process deviations and potential correlation with AEs in hospitalised patients who are treated according to a protocolised care pathway, in this case patients who suffer from an acute myocardial infarction (AMI). The developed method to assess AEs in acute MI patients, is based on the Harvard Medical Practice Study (HMPS), which is a structured patient record review that has also been used in other AE-studies.^{4 16 18 19} This current manuscript describes how this commonly used method is adapted for our specific patient

population. In addition, it was examined whether the linkage between process deviations and AEs will increase the uniformity of the assessments of AEs and creates the possibility to develop better improvement strategies.

METHODS

Patient population

Patients who were admitted in 2012 and 2013 to the Leiden University Medical Center with an acute myocardial infarction warranting coronary angiography (CAG) or percutaneous coronary intervention (PCI) and treated according to the MISSION!-Protocol were included.²⁰ The Leiden University Medical Center functions as a tertiary referral center performing PCI procedures on a 24/7 basis and serves an area of approximately 750,000 inhabitants. The MISSION!-protocol contains a prehospital, in-hospital, and outpatient framework for clinical decision making and treatment for the different diagnosis in acute myocardial infarctions (unstable angina (UA)), ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI)). This study focussed on the in-hospital program (early reperfusion, same diagnostic trajectory like 2D-echocardiography, structured medical therapy, and disease education). Generally, patients are planned for discharge 12 hours after a coronary angiography, or 48 hours after a percutaneous coronary intervention. The MISSION!-protocol is based on the evolving guidelines of the European Society of Cardiology.²⁰⁻²² The MISSION!-patient records were extracted from the electronic patient file system (EPD-Vision, LUMC, Leiden The Netherlands) by selecting the diagnose coding of a diagnosis-treatment-combination for UA (11.203), STEMI (11.204) and NSTEMI (11.205). Patients with any of these three diagnose-codings were linked with the clinical database to select the patients who received an intervention procedure (CAG or PCI) within 24hrs after admission. This was applied to all patients admitted to the LUMC between January 1, 2012 and December 31, 2013. Patients with an urgent coronary artery bypass grafting after CAG or urgent PCI were excluded because they underwent a different treatment path.

Review Process

The method used in this study was based on a protocol originally developed by the Harvard Medical Practice Study. A modified version of this protocol was used in studies in Australia, Canada, Denmark France, New Zealand, the United Kingdom and the United States.^{3 5 10 11 13 14} A Dutch protocol, based on the Canadian Adverse Events study, was used in studies in 2004, 2008 and 2011/2012.^{15 16 19} To identify high risk patient records, the Harvard Medical Practice Study developed 18 triggers (i.e. "Unplanned return to the operating room" or "Hospital-incurred patient injury"). The presence of one or more of

these 18 triggers was established in Phase 1. In case a trigger was found, the patient record entered a second phase, which focused on identifying whether harm was done to the patient, whether the harm was due to the care that the patient received, and whether the harm was preventable. To increase the uniformity of the assessment of AE and to gain more insight into patterns of adverse events, the triggers of the Harvard Medical Practise Study were specified for acute cardiac care, thereby creating the opportunity to identify specific process deviations. In the first phase of the review process we focused on identifying these process deviations in the patient records, and in the second phase AEs were identified. In case an AE was identified, it was also scored on preventability.³

Phase I: specification of process deviations for AEs

In the MISSION!-protocol, the patient can have different workflows according to their electrocardiographic-diagnosis at admission (ST-elevation myocardial infarct, non-ST-elevation myocardial infarction or unstable angina). In the search for adverse events all process deviations from the MISSION!-protocol were identified. During this review-phase, a process deviation was defined as every operation or treatment that differed from the MISSION!-protocol, such as additional procedures (a pacemaker implantation or second PCI), prescription of extra medication other than described in the protocol (use of anti-aritmica, anti-coagulation, inotropics or diuretics) or omission of a procedure (no diagnostics performed). If a patient had a transient heart rhythm disorder without treatment consequences, the process deviation was noted as an observation of the heart rhythm.

Figure 1 shows all the defined process deviations. The review process of all medical records (nursing and medical records) was performed by a physician with work-experience at the clinical department and who is familiar with reviewing electronic files. In contrast to the original triggers of the Harvard Medical Practice Study and other process deviation frameworks like the Process Deviations Analysis Framework, no judgements were made during Phase 1 on whether the process deviation were 'unexpected' or 'unplanned'.²³ After identifying all process deviations, the process deviations were categorised into main categories and translated back to one (or more) of the original 18 triggers of the Harvard Medical Practice Study. Because of the defined inclusion criteria stated in the MISSION!-protocol and restrictions concerning the availability of data from the patient records in the peripheral hospitals up to 30 days after discharge, it was decided beforehand that events experienced prior to (i.e. unplanned admission before index admission), or after the index admission (i.e. readmission) were excluded from the review process.

Phase II: Determination of an adverse event and preventability

During phase two the nursing and medical records of the admission were reviewed for adverse events by a clinical physician. If applicable, also the records of patients who were

transferred to another hospital during their admission were traced. In case the physician found more than one AE in a patient, they were separately registered.

Event classification

First it was assessed whether the event resulted in harm to the patient. The definitions are mentioned in **Supplementary file 1**. If the patient experienced harm that resulted in any disadvantage for the patient, such as prolonged admission, temporary or permanent (physical and/or mental) impairment or death, it was rated whether the harm was caused by health care (i.e. an adverse event) and if so, whether it was preventable (i.e. caused by an error). Both the causation and the preventability were scored on a 6-point-Likert scale. Preventability of the AE was assessed by indicating a score between 4 and 6 on the Likert scale. This is in accordance with other AE studies.**(Supplementary file 2 and 3)**

To support the reviewer in the rather implicit judgement of determining the causation in health care of the AE, the causation score was preceded by structuring questions to direct if the injury was indeed caused by medical care rather than the underlying acute coronary syndrome. **(Supplementary file 2 and 3)** For example: *“Does the timing of the (adverse) event suggest that the injury is related to the treatment?”* and *“Is the lack of treatment or delayed treatment a recognised cause of this injury?”* Analogously, preceding questions were used to judge if an adverse event was preventable. An adverse event was found to be preventable when the **performance of the practitioner** fell short of the expected **level** of competence based on the professional standard. Appropriate management of the myocardial infarction was outlined in the previously mentioned MISSION!-protocol. Also local hospital guidelines on precautionary measures to prevent common events, such as measures to prevent a delirium, were taken into account by the reviewer and the expert panel. The questions preceding the preventability score were also used to evaluate the complexity of the medical history and comorbidity of the patient. In addition, it was of importance to consider the potential benefit of the procedure, the calculated risk, and the degree of emergency in treating a patient with a myocardial infarction. Therefore, the original preceding questions were augmented by two extra questions on whether the management of the AMI was appropriate, and on the estimated risk of an adverse event associated with the management.**(Supplementary file 3)**

Expert panel

In case of doubt regarding the causality and/or the preventability of an event, an advisory opinion of an expert panel was requested. The expert panel consisted of two consultants, cardiologists with a wide range of experience in interventional cardiology or electrophysiology. Both cardiologists were either involved in managerial tasks or departmental incident analysis. In addition two cardiologists in their final year of training and involved in the daily

New process deviations		Category	Related Harvard Medical Practice Study Triggers
Observation	Observation - Physical or mental complaints.	OBSERVATION	Any other undesirable outcome not covered above.
Observation	Observation - Rhythm or conduction disorders.	79	Unplanned return to the operating room.
Diagnostic	Diagnostic - Consultation of other specialism.	79	Unplanned removal, injury, or repair of organ during surgery.
Diagnostic	Diagnostic - CT-scan	27	Hospital-acquired infection or sepsis (initiated > 72 hours after admission).
Diagnostic	Diagnostic - Infectious.	1	Other patient complication (no natural consequence of disease).
Diagnostic	Diagnostic - Ultrasound of the groin.	14	Development of neurological deficit not present on admission.
Diagnostic	Diagnostic - Other, not specified before.	18	Hospital-incurred patient injury (Permanent or temporary injury obtained (acquired) during index admission).
Therapy	Therapy - Anti-arrhythmia.	280	Adverse drug reaction.
Therapy	Therapy - Anticoagulation.	7	Cardiac or respiratory arrest.
Therapy	Therapy - Blood transfusion.	26	Unexpected death.
Therapy	Therapy - Consultation of other specialism.	11	Unplanned transfer from general care to intensive care (unit).
Therapy	Therapy - Diuretics.	14	
Therapy	Therapy - ICD-implantation.	23	
Therapy	Therapy - Infectious.	8	
Therapy	Therapy - Inotropics.	15	
Therapy	Therapy - Medication error.	12	
Therapy	Therapy - Palliative care	1	
Therapy	Therapy - Pericardial drainage.	4	
Therapy	Therapy - Positioning of a temporary cardiac pacing wire.	6	
Therapy	Therapy - Positioning of an intra-aortic balloon pump.	14	
Therapy	Therapy - Return to catheterization room for a new procedure (CAG or PCI)	14	
Therapy	Therapy - Resuscitation	42	
Therapy	Therapy - Thrombin injection.	17	
Therapy	Therapy - Rhythm or conduction disorders (incl. pacemaker implantation).	17	
Therapy	Therapy - Other, not specified before.	9	
Therapy	Therapy - Other, not specified before.	40	
Logistic	Logistic - IC-transfer.	29	
Logistic	Logistic - Other, not specified before .	17	
Logistic	Logistic - Other, not specified before .	12	
The colours of the process deviation category corresponds with the Harvard Medical Practice Study Triggers. CAG = coronary angiography; CT = computer tomography; PCI = percutaneous coronary intervention; IABP = intra-aortic balloon pump; ICD = implantable cardioverter-defibrillator; IC = intensive care.			

Figure 1: Newly defined process deviations in relation to the original Harvard Medical Practice Study.

clinical practice formed part of the expert panel. In case there was a discrepancy about the causation or preventability between the reviewer and the expert panel, the structuring questions were used to guide the discussion and reach a final decision. **(Supplementary file 2 and 3)** The expert panel was also involved in reaching consensus on the causality and preventability of events, which frequently occurred such as a groin hematoma.

Privacy

Guarding privacy and anonymity were considered to be a high priority. To warrant the privacy and anonymity all people involved in the study signed a confidentiality agreement to maintain the confidentiality of the information. Study results were stored in a Microsoft Access 2010 Database® on a safety disk which can only be accessed by individuals who are involved in the study.

Ethical approval

The Leiden University Medical Center gave a declaration of “medical-ethical permittance not necessary” for this retrospective records study (reference number P15.133). The peripheral hospitals, had formally consented to obtain data from outpatient clinical records, in accordance with their local medical-ethical committee.

ANALYSIS & STATISTICS

Patient characteristics and process deviations

For all patients, baseline characteristics such as age, sex, medical history and admission characteristics like length of stay, comorbidities, cardiac diagnosis and procedural characteristics (stenting or not) were retrieved. Continuous variables are presented as mean with standard deviation or median with 25th and 75th percentile, where appropriate. Dichotomous variables are presented as numbers and percentages. The number of process deviations within each main category were calculated by summing the number of process deviations of each subcategory, after which they were plotted in a pie chart. Baseline comparability between patients with or without an process deviations were evaluated by descriptive statistics and Independent T-test or Chi-square test, when appropriate. A p-value smaller than 0.05 was considered to be statistically significant. Furthermore, the *process deviation : AE ratio* was determined to assess the effectivity of the new method based on identifying process deviations, and a Chi-square analysis was performed to assess differences between patients with and without process deviations.

Inter-rater reliability

To assess the reliability of the assessment of the presence and preventability of an AE of the first reviewer, 10% ($n = 87$) of the patient records were independently screened by an experienced cardiologist from another center. This second reviewer was blinded to the outcome of the first review. To maximize efficiency, stratified sampling was performed. AE positive patient records were oversampled in relation to AE negative patient records, with a ratio of 2:1 (AE : non AE). These patients were randomly selected from the whole MI study population. Consecutively, all patient records that contained an AE according to both reviewers were also reviewed on preventability. The percentage of agreement on causality and preventability is determined on a patient-level and expressed separately for positive and negative rating. In addition, Cohen's kappa-statistics was calculated.²⁴ To avoid any potential bias in the kappa's coefficient, caused by the stratified sampling, the kappa-statistics were also calculated separately for the patient records with and without an AE.

Data accuracy

Data accuracy (missing data, inconsistent data) was checked on a regular basis and analysed using Microsoft Access 2010 and IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.

RESULTS

Process deviations and adverse events

In total 879 patients (age 64 ± 12 years, 71% male) were reviewed, including the follow-up records of 274 patients who were transferred to three affiliated hospitals after a cardiac procedure in the tertiary care center. **(Table 1)** In 347 patients (39%) one or more process deviations during admission (587 deviations in total) were found. The process deviations ($n = 587$) were categorised into four main categories: observation, diagnostic, therapy, or transfer. **(Figure 2)** Most process deviations were found during observations (especially observation of mental and physical complaints or rhythm disorders) and therapy (especially anticoagulation therapy or return to catheterisation room for a second CAG or PCI procedure). **(Figure 1)** Patients with one or more process deviations were significantly older than patients without a process deviation (67 ± 12 vs 61 ± 11 , $p < 0.001$). In addition, female patients (66% vs 75% male patients, $p = 0.006$) and patients with a lower renal function had a significantly higher risk for process deviations. **(Table 1)**

Translation of triggers to process deviations

After categorising the process deviations, the categories were translated back to one (or more) of the 18 original triggers of the Harvard Medical Practice Study. **(Figure 1)**

Due to the inclusion criteria of the study population, original triggers like *“unplanned admission before index admission”*, *“unplanned transfer to another acute care hospital”*, *“injury related to abortion or delivery or neonatal complications”* were not applicable to this population. Moreover, *“inappropriate discharge to home”* and *“unplanned readmission after discharge”* were not included because the medical records were only reviewed while the patient was admitted to the hospital. Triggers like *“dissatisfaction with care documented in the medical record”* and *“documentation or correspondence indicating litigation”* were not used if they did not result in an alteration of the workflow. Eleven original triggers remained. Especially triggers used for diagnostic or therapy procedures became more specified by using process deviations (*“Unplanned return to the operating room”*, *“unplanned removal, injury, or repair of organ during surgery”*, and *“Other patient complication (no natural consequence of disease)”*). Likewise, the trigger *“Unexpected death”* was more specified in process deviations as *“Resuscitation”* or *“Positioning of an intra-aortic balloon pump”*.

In 116 patients, 33% of all patients with a process deviation, an adverse event was found. The majority of patients with an adverse event had more than one process deviation (64 of 116 patients (55%), average of 2.0 ± 1.7 process deviations per patient). In the group of patients with no adverse event (150 of 231 patients (65%)) had more than one process deviation, average of 1.5 ± 0.9 process deviations per patient) ($p = 0.005$). No significant differences were found in patients with and without an adverse event in the distribution of the type of process deviations. **(Table 2)** Likewise, no differences in mortality-rate (5 of 116 AE patients died (4.3%) vs. 13 of 763 non-AE-patients (1.7%), $p = 0.065$). All patients who died ($n = 18$, 2.0%) during their hospital stay, experienced a process deviation ($n = 23$ in 18 patients) and 5 patients an adverse event. The process deviations that were found in deceased patients were mainly related with Therapy (21) or Transfer (2) and no differences were seen between deceased patients with and without an adverse event in the type of process deviation (4 of 5 Therapy deviation in AE patients vs. 17 of 18 Therapy deviation in non-AE patients, $p = 0.395$). In patients without a process deviations, 2 patients (2 of 532, 0.4%) experienced a non-preventable adverse event.

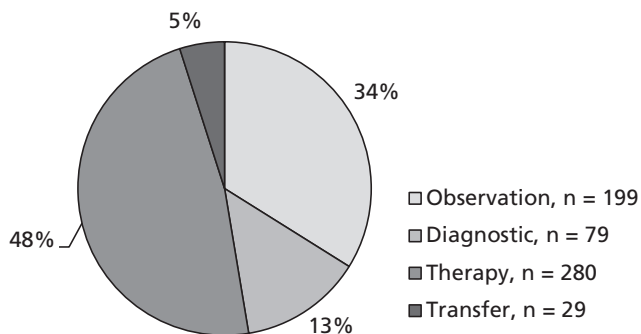
Inter-rater reliability

The inter-rater reliability assessment was carried out for 87 patients (10% of $n = 879$) by a second, independent cardiologist with experience in the assessment the presence of preventable adverse events by means of medical record reviewing. On a patient level, there was an agreement in 73 patient record (agreement level of 84%). The positive agreement on the presence of an adverse event in the patient records was 87%, and the negative agreement on the absence of an adverse event in the patient records was agreement 80%. No differences were found when performing an independent analysis of the agreement

Table 1: Baseline characteristics

	All patients N = 879	With process deviation N = 347	No process deviation N = 532	p-value
Demographic characteristics				
Age (years)	64 ± 12	67 ± 12	61 ± 11	≤ 0.001
Male sex	626 (71%)	229 (66%)	397 (75%)	0.006
BMI (kg/m ²)	27 ± 4	26 ± 4	27 ± 4	0.070
Length of stay (days) (median, IQR)	3 (2-4)	3 (2-5)	2 (2-3)	≤ 0.001
Comorbidities				
Hypertension	352 (40%)	155 (45%)	200 (38%)	0.066
Hyperlipidemia	198 (23%)	75 (22%)	123 (23%)	0.625
Diabetes mellitus	115 (13%)	52 (15%)	63 (12%)	0.177
Known coronary disease	145 (16%)	65 (19%)	80 (15%)	0.147
Known pulmonary disease	88 (10%)	43 (12%)	45 (8%)	0.055
Renal clearance (ml/min/1.73m ²)	75 ± 23	72 ± 25	77 ± 22	0.002
Infarct characteristics				
Diagnosis				0.052
STEMI	594 (68%)	234 (67%)	360 (68%)	
NSTEMI	135 (15%)	63 (18%)	72 (14%)	
UAP	114 (13%)	34 (10%)	80 (15%)	
Other	36 (4%)	16 (5%)	20 (4%)	
Treated with PCI	747 (85%)	297 (86%)	450 (85%)	0.684

BMI = body-mass index; IQR = Interquartile range; STEMI = ST-elevated myocardial infarction; NSTEMI = non-ST-elevated myocardial infarction; UAP = unstable angina pectoris; PCI = percutaneous coronary intervention.

**Figure 2:** Five hundred and eighty-seven process deviations of all 879 patients.

in patient records with AE and without AE (independent analysis AE positive agreement 86%, independent analysis non-AE: negative agreement 98%). In 45 patients preventability was assessed on which there was an agreement of 84%. The kappa statistics of the preventability was substantial (κ 0.67 (95%CI 0.45 - 0.90)). **(Table 3)** Notable, a common type of adverse event was a groin complication (groin hematoma), on which consensus was established by the expert panel. In principle, a groin hematoma was judged to be preventable. The expert panel decided that despite adequate action, a groin hematoma is less preventable in high risk frailty groups like obese, restless, elderly and patients with known peripheral vascular disease when using dual antiplatelet therapy.

DISCUSSION

This study describes the development of a new valid screening tool for identifying process deviations and AEs in a specified patient population; patients with an acute myocardial infarction, treated according to a strict defined protocol.

First of all, process deviations were identified. We reviewed 879 patient records in which 587 process deviations in 347 patients were found. In 116 patients, 33% of all patients with a process deviation, an adverse event was found, leading to an *AE : process deviation* ratio of 1 : 3. This ratio seems higher in comparison to other studies where one adverse event was found in every sixth or seventh patient record with a trigger.^{3 4 18} However, it is important to take into account that previous studies were focused on a wider range of specialties, which can explain a lower prevalence of AE's. Interestingly, the type of process deviation is not associated with experiencing an AE; no differences in the type of process deviations were found between patients with an adverse event compared to patients without an adverse event. This finding could be explained by the fact that, despite process

Table 2: Comparison of process deviations.

	Process deviations in all patients	Process deviations in all patients without an adverse event	Process deviations in all patients with an adverse event	p-value
Process deviations	N = 587	N = 354	N = 233	
Number of patients	879	231	116	
Observation	199 (34%)	124 (35%)	75 (32%)	0.477
Diagnostic	79 (13%)	46 (13%)	33 (14%)	0.685
Therapy	280 (48%)	163 (46%)	117 (50%)	0.322
Transfer	29 (5%)	21 (6%)	8 (3%)	0.172
None	532	n/a	n/a	n/a

deviations are present in a patient record, they may not be the root cause of the AE. Various preventive actions may have taken place after the occurrence of the process deviation which could have averted patient harm. In addition, AEs are more likely to be caused by a combination of multiple factors.²⁵ This makes it difficult to develop a targeted approach to improve patient safety. More research, for instance based on incident analysis methods using more sources of information than the patient record only, may help to identify other variables (i.e. patient characteristics) that predict an AE. The majority of process deviations were found during clinical observation and therapy, which is in line with prior studies using the related original HMPS triggers.^{17 18}

Based on the inter-rater reliability that was found in this study (causality and preventability agreement are both 84%), this adapted method appears to be a reliable and suitable instrument to use in this well-defined patient population. In previous studies, the reliability of the occurrence of an AEs in general hospitals was moderate to substantial (kappa ranged from 0.42 – 0.83, agreement ranged from 76% to 92%), and if measured, it was moderate for determining the preventability of AEs (kappa ranged from 0.33 – 0.69, agreement ranged from 68% to 91%).**(Supplementary file 4)**^{3 4 8 11 13 18 26-29} Recently a study focussed on hip fractures in elderly patients showed an agreement of 85% in the presence of an AE, with a k-value of 0.52.³⁰ The substantial reliability in the current study suggests that an assessment procedure shows reduced inter-rater variation when being performed in a specified population with a strictly pre-defined protocol. Nevertheless, a 100% agreement score was

Table 3: Assessment of the inter-rater reliability between two physicians.

Causality	87 patients
Agreement	84%
Positive agreement	87%
Negative agreement	80%
Kappa statistic (95% CI)	0.67 (0.51 – 0.83)
Preventability	45 patients
Agreement	84%
Positive agreement	87%
Negative agreement	80%
Kappa statistic (95% CI)	0.67 (0.45 – 0.90)

To assess the reliability of the preventability, the sample size population contained an overrepresentation of adverse events compared with the whole MI study population (AE:non AE ratio is 2:1).

not reached. This is probably due to the different perspectives of physicians and limitations in our medical knowledge in causal relations, therefore the assessment of preventability remains under debate until new scientific evidence is discovered. Previous studies on AEs

were performed in general hospital populations and encountered a large variation among specialities with regard to the risk of the procedures employed and the severity of illness of the patients. As a result, heterogeneous numbers and causes of (preventable) AEs were reported among the different specialities.^{4 8 18 26} Focussing on one specific illness leads to a decrease in the workload for the hospital staff, makes it easier to plan the collection of data, and limits the interruption of the work flow. In the end, this specific instrument is likely to provide more valuable insights into the specific cause of an AE in myocardial patients and consequently, possibilities to improve patient safety. Similar, adverse events can show recurrent wrong patterns in the management within a clinic department.

Some limitations of the proposed method have to be considered. First, the validation method of the new process deviations tool can be considered incomplete because there was no direct comparison with an alternative screening tool, such as the original HMPS trigger tool. Therefore, we cannot exclude the possibility that other numbers of process deviations or triggers were found if a comparison using another tool was performed. In addition, tools for identifying process deviations, such as the Process Deviations Analysis Framework or the (Lean) Six Sigma Model, were not used for the design of the current method because they are not (yet) suitable for assessing whether process deviations are associated with undesirable (health care) outcomes.^{23 31} Besides, there are still considerable challenges when it comes to implementing process deviations frameworks in a healthcare setting. Current process deviation frameworks are highly measurement- and data driven while a health care setting is mostly depended on human behaviour, which is difficult to quantify. Another limitation is that this study depended exclusively on documentation in medical and nursing records. However, the likelihood that this has affected the quality of our study is low since previous studies showed that a record review method is sensitive for identifying AEs.³² Also, direct comparison of these results with different hospitals is difficult, as record reviewing highly depends on the level of record completeness and the use of a (electronic) patient record. To lower the possibility of hindsight bias, a prospective design with a weekly review process of a researcher can be considered.^{8 33}

Future implications

In the future it could be of interest to explore whether application of this new method makes it possible to assign AEs to uniform groups after which action can be taken. Furthermore, the eventual goal is to monitor patient safety with real-time process deviations and adverse events measurements, or even better, to predict which patients are at risk for AEs to prevent harm. For this next step, existing approaches for measuring process deviations used in other fields can be helpful. An integration of HMPS and Lean Six Sigma, for example, may be beneficial for healthcare. HMPS's strength is to structure implicit relations and to define harm, on the other hand Lean Six Sigma is a data-driven approach, which

may facilitate detection of process deviations as indicators of adverse event. It should be explored whether it is possible to develop an electronic tracking system, as part of an electronic patient records system, which enables the continuous monitoring of care. This will shift the emphasis away from focusing solely on medical errors, and more on real-time performance and measures that relate to future risks and resilience of organisations. This could be the starting point for the development of a hospital benchmark Quality Instrument to objectify patient safety as part of quality of care in a specific patient population.³⁴ Bottom-up, this could serve as an incentive to improve safety and top down it will give insight to redesign patient work-flows which can improve efficacy and quality of care. Structural process deviations seem more useful for educational purposes compared to individual preventable incidents. Although this method is focussed on one illness, this approach may also be applied to other patient populations, or to evaluate other care tracks like the MISSION!-protocol, for example the total hip arthroplasty procedures.¹⁷

CONCLUSION

In conclusion, this paper describes the development of a reliable method to objectively assess the process deviations and the occurrence of AEs in a specified population.

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An **adverse event** is (1) an unintended injury (physical and/or mental) which results in (2) temporary or permanent disability, death or prolonged hospital stay and (3) that is caused by health care management rather than by the patient's underlying cardiac disease.

Unintended injury refers to any disadvantage for the patient that leads to prolonged or strengthened treatment, temporary or permanent (physical and/or mental) impairment or death.

Disability refers to temporary or permanent impairment of physical or mental function attributable to the adverse event (including prolonged or strengthened treatment, prolonged hospital stay, readmission, subsequent hospitalisation, extra outpatient department consultations or death).

Causation refers to injury caused by health care management including acts of omission (inactions) i.e. failure to diagnose or treat, and acts of commission (affirmative actions) i.e. incorrect diagnosis or treatment, or poor performance.

Health care management includes the action of individual hospital staff as well as the broader systems and care processes. Health care management is any care related activity that involves the delivery of care or monitoring of health which is provided by individuals or a team of professionals.

Preventable adverse event is an adverse event resulting from an error in management due to failure to follow accepted practice at an individual or system level. Accepted practice was taken to be 'the current level of expected performance for the average practitioner or system that manages the condition in question'.

Process deviation was defined as every operation or treatment that differentiated from the MISSION! Protocol.

Supplementary file 1: Definitions

Preceding questions:

1. Does the timing of events suggest that the injury is related to the treatment or to the lack of treatment? (Likely/Possibly/Unlikely/Not applicable)
2. Is there a note in the medical record indicating that a health care professional or health care management caused the injury? (No/Yes/Not applicable)
3. Is there a note in the medical record suggesting the possibility of an unintended injury from the patient's disease? (No/Yes/Not applicable)
4. Are there other reasonable explanations for the cause of the unintended injury? (No/Yes/Possibly/Not applicable)
5. Is the lack of treatment or delayed treatment a recognized cause of this injury? (Widely recognized/Recognized by other specialists/No/Not applicable)
6. Is the lack of diagnosis or delayed diagnosis a recognised cause of this injury? (Widely recognized/Recognized by other specialists/No/Not applicable)
7. Is this injury a recognized complication of the patient's underlying index disease? (Widely recognized/Recognized by other specialists/No/Not applicable)

A score on ***causation*** was given on a 6 point Likert scale:

1. (Virtually) no evidence for health care management causation.
2. Slight to modest evidence of health care management causation.
3. Health care management causation not likely (less than 50/50, but 'close call').
4. Health care management causation more likely (more than 50/50, but 'close call').
5. Moderate to strong evidence of health care management causation.
6. (Virtually) certain evidence of health care management causation.
Counted as caused by healthcare if the score was 4 to 6.

Supplementary file 2: Causation score

Preceding questions:

1. How complex was this case? (Very complex/Moderately complex/Somewhat complex/Not complex/Unable to determine)
2. What was the co-morbidity of the patient? (Significant co-morbidity/Moderate co-morbidity/Mild co-morbidity/No co-morbidity)
3. What was the degree of deviation of management of the primary illness (not the adverse event) from the accepted norm? (Severe/Moderate/Little/None)
4. What potential benefit was associated with the management of the illness which led to the Adverse Event? (Life saving/Curing/Life prolonging/Symptom relief/Palliation//No potential benefit)
5. What was the degree of emergency in management of the primary illness (not the adverse event) prior to the occurrence of adverse event? (Very urgent/Moderately urgent/Not urgent)
6. Did the patient have any follow-up as a result of this Adverse Event? (No/Counselling/Psychiatric/Rehabilitation/Routine clinical/Other/UTD)

Preparatory questions, added to the protocol:

7. Was the management of the primary illness (not the adverse event) appropriate? (Definitely appropriate/Possibly appropriate/Probably appropriate/Definitely not appropriate)
8. What was the risk of an adverse event related to the management ? (High/Moderate/Low/Not applicable)

A score on ***preventability*** was given on a 6 point-Likert scale:

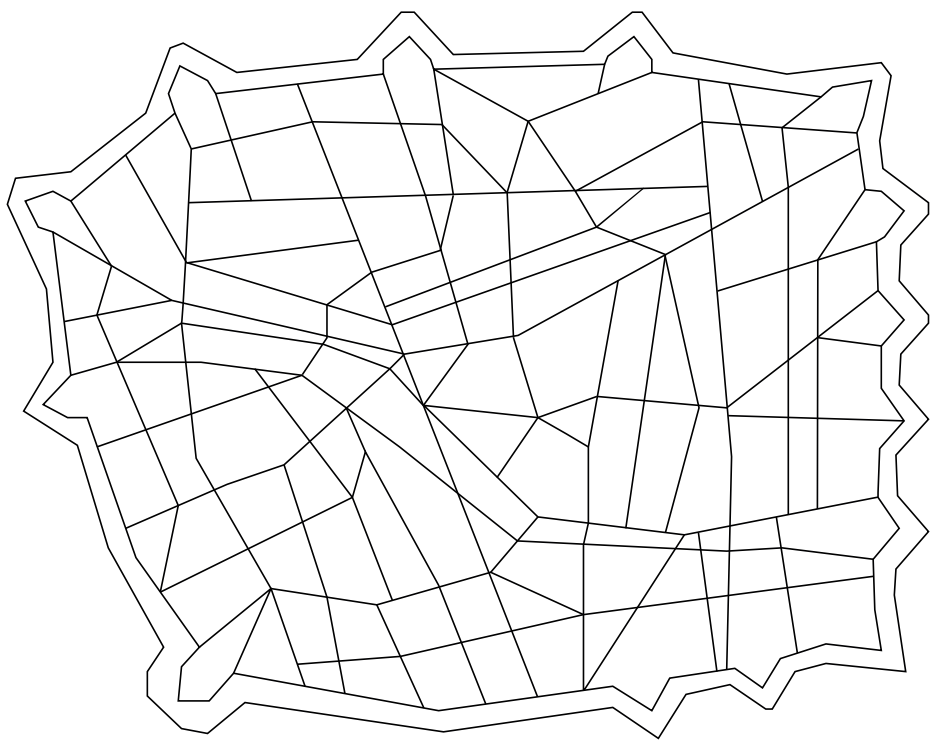
1. (Virtually) no evidence for preventability.
2. Slight to modest evidence of preventability.
3. Preventability not quite likely (less than 50/50, but 'close call').
4. Preventability more than likely (more than 50/50, but 'close call').
5. Strong evidence of preventability.
6. (Virtually) certain evidence of preventability.

Counted as preventable if the score was 4 to 6.

Supplementary file 3: Preventability score

Supplementary file 4: Comparison of inter-rater variability in other adverse events studies.

Author	Year	Country	Causality		Preventability	
			Kappa statistics	(95%CI)	Agreement	Kappa statistics (95% CI)
Brennan	1991	United States of America	0.61		89%	
Wilson	1995	Australia	0.42			0.33
Thomas	2000	United States of America	0.40 (0.3 – 0.5)		76%	
Baker	2004	Canada	0.45 (0.33 – 0.57)			0.69 (0.55 – 0.83)
Michel	2007	France	0.83 (0.67 – 0.99)		92%	0.31 (0.05 – 0.57)
Sari	2007	United Kingdom	0.64		86%	0.33
Soop	2009	Sweden	0.80		91%	0.76
Zegers	2009	The Netherlands	0.25 (0.05 – 0.45)		76%	0.40 (0.7 – 0.73)
Hogan	2012	United Kingdom	0.54 (0.37 – 0.71)			
Baines	2013	The Netherlands	0.47 (0.33 – 0.61)		83%	0.49
Merten	2015	The Netherlands (focus hip fractures)	0.52		85%	too small (4 cases)



Chapter 3

The occurrence and preventability of adverse events in patients with acute coronary syndrome.

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Submitted

ABSTRACT:

AIM: Adverse events as a result of hospital care occur frequently. However, data on adverse events in acute care settings are scarce. Hence, our aim is to gain insight in the occurrence and preventability of adverse events and to identify patients at increased risk for an adverse event in acute cardiac care.

METHODS & RESULTS: Patients ($n = 879$, 64 ± 12 years, 71% male) presenting with an acute coronary syndrome in a tertiary care center warranting coronary angiography in 2012 and 2013 were included. Trained physicians performed a structured patient record review to screen for the nature, occurrence and preventability of adverse events during admission. During 2,999 days of admission, 143 adverse events occurred in 116 patients (13%), of which 35 (3%) were considered to be preventable. Older age, female sex and decreased renal function were predictors of adverse events in patients with a coronary syndrome.

CONCLUSION: Harm due to health care is a serious problem in ACS patients. Research on patient safety on a departmental level is important, and safety should be considered a core value in a care organization.

INTRODUCTION

The primary goal of medical care is to discharge the patient in the best possible health condition, thereby avoiding harm and subsequent hospitalizations. Unfortunately, medical care sometimes results in (potentially preventable) medical errors, disability or death, emphasizing that patient safety can still be improved.¹ Since the publication of the *To Err is Human* report in 1999 by the National Academy of Medicine, an increased sense of urgency to improve patient safety resulted in increasing numbers of hospital safety programs.² Motivated by success stories of non-medical industries, such as aviation and chemical industries, the first retrospective patient record review study was conducted as part of the Harvard Medical Practise Study, after which many studies in different countries followed that conducted patient record reviewing on a national level. These studies reported harm due to healthcare (e.g. adverse event (AE)) rates of 2.9 % to 16.6% based on all admissions. In addition, these studies found a significant number of patients experiencing death or permanent disability due to healthcare management errors, rather than due to the underlying disease process.^{1, 3-11} Notably, a significant part of these AEs were deemed preventable (20-70%).

Currently, the focus seems to be shifting from patient record review on a hospital or national level to record reviewing on a departmental or disease-specific level as this might provide more insight into specific potential improvement opportunities. Especially strictly defined care programs, like the care for acute coronary syndrome (ACS) patients, seem to be suitable for record review. These programs have structured and clearly defined steps of procedures and interventions, which are in some way comparable to applying Lean Six Sigma in other industries. Hence, deviations from this care program might suggest potential care problems or a lack of efficiency and can therefore provide a unique starting point to examine opportunities to optimize the care program and improve patient safety¹². We recently published a study describing the development of a validated method for patient record reviewing, based on identifying deviations in the care process of a strictly defined care program, in a patient population with ACS.¹³ Hence, this method offers an opportunity to gain insight in the occurrence and preventability of AEs and to identify patients at increased risk for an AE.

METHODS

Patient population

Since 2004, all patients admitted to Leiden University Medical Center on suspicion of an ACS warranting coronary angiography, are evaluated and treated according to a strict

protocol (the MISSION! Protocol), based on evolving guidelines as was previously described in detail.¹⁴⁻¹⁶ For the current study, patients treated in 2012 and 2013 for unstable angina (UA), non-ST-segment elevation myocardial infarction (NSTEMI) and ST-segment elevation myocardial infarction (STEMI) were selected, based on the discharge diagnosis.

STEMI was defined in the presence of symptoms of angina lasting longer than 30 minutes with typical electrocardiographic changes (ST-segment elevation ≥ 0.2 mV in ≥ 2 contiguous leads in V1 through V3, or ≥ 0.1 mV in other leads, or presumed new left bundle branch block).¹⁷ An NSTEMI patient showed elevated biomarkers, but showed no ST-elevation during admission. Patients without elevated biomarkers were diagnosed as unstable angina.

The current study focussed on the in-hospital program (early reperfusion, diagnostic trajectory like echocardiography, structured medical therapy, and disease education). At the time of inclusion the preferred approach for angiography in this study population was femoral access. Patients treated with coronary artery bypass grafting were excluded for the current analysis, since the standard protocol could not be followed. The study protocol was approved by the Medical Ethics Committee of the Leiden University Medical Center, The Netherlands. The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Evaluation for adverse events

A structured medical record review, based on the method of the Harvard Medical Practice Study, to assess the occurrence and preventability of AEs was performed by two trained independent physician reviewers.¹⁰ A comprehensive description of the method and the prior screening of process deviations and its inter-rater reliability was reported previously.¹⁸ In brief, the first phase involved a medical record review of process deviations. A process deviation was defined as every procedure or treatment that differed from the MISSION!-protocol, such as additional procedures (a pacemaker implantation or second percutaneous coronary intervention), prescription of extra medication other than described in the protocol (use of anti-arrhythmic drugs, anti-coagulation, inotropics or diuretics) or omission of a procedure (no diagnostics performed). If a process deviation was present, the patient record entered a second phase in which an assessment was performed on whether the event resulted in harm to the patient. Patient harm or any disadvantage for the patient that resulted in prolonged or strengthened treatment, temporary or permanent (physical and/or mental) impairment or death and caused by medical care was defined as an AE. If so, it was rated whether it was preventable (and therefore caused by an error). The causation score of an AE, as well as the preventability score, were scored on a 6-point-Likert scale and noted as caused by health care or preventable if the score was 4 to 6. When more than one AE occurred in a patient, both were registered. The inter-rater reliability was

assessed for 10% of the patients (n=87) by an independent cardiologist, who was blinded to the outcome of the first review. On a patient level, there was an agreement in 73 patient records (agreement level of 84%). The κ statistics of the causality was substantial (κ 0.67 (95% CI 0.51 to 0.83)).¹³

Classification of an adverse event

AEs were classified by severity (leading to possible injury, temporary injury, permanent injury or death), nature (e.g. as a consequence of taken medication, procedural activities, diagnostic activities or other clinical activities) and causal factors (technical, human, organizational or patient-related factors) were noted.¹⁹ In case the assessment of the physician reviewer(s) was inconclusive, an expert panel, consisting of four experienced cardiologists, was consulted in order to come to an agreement regarding the causality or preventability. Examples of the classification of preventable adverse events are shown in **Table 1**.

Clinical characteristics

Clinical characteristics were added to the protocol to correlate clinical parameters with AEs. Infarct characteristics were collected, such as diagnosis, percutaneous treatment, peak troponin-T and creatine kinase. Furthermore, comorbidities such as hypertension (defined as blood pressure $\geq 140/90$ mmHg or previous pharmacological treatment), hyperlipidaemia (defined as total cholesterol ≥ 190 mg/dl or previous pharmacological treatment), a diagnose of diabetes mellitus (insulin and non-insulin-dependent), history of pulmonary diseases and renal clearance (calculated with the Chronic Kidney Disease Epidemiology Collaboration equation, presented in $10 \text{ mL/min/1.73m}^2$) at admission were noted.²⁰

Statistical analysis

Continuous variables are presented as means with standard deviations or medians with 25th and 75th percentiles where appropriate. Dichotomous variables are presented as numbers and percentages.

AE rates were reported by the proportion of patients with at least one AE and the number of AEs per 1,000 patient days. In the calculation of the 95% confidence interval (95%-CI) for event rates, a Poisson distribution of the observed number of events was presumed. To obtain a risk estimation of experiencing an AE, demographic variables and comorbidities known at baseline were used to conduct a logistic regression. First, the baseline variables are studied in a univariate logistic regression model, with experiencing an AE as binary outcome. For each variable an odds ratio with a p-value and 95%-CI was calculated. Variables with a p-value ≤ 0.10 are further evaluated in a multivariate logistic model, using backward stepwise selection. At each step, the least significant variable was discarded from the model, until all variables in the model reached a p-value ≤ 0.05 .

Table 1: Examples of the determination of an preventable adverse event.

Nature	Example of a preventable adverse event
Diagnostic activities	<i>Despite evolving electrocardiographic changes during the weekends, percutaneous coronary intervention was delayed.</i> Human factors as causal factor of the event.
Drug-related adverse event	<i>Hypotensive episode after a double dose of antihypertensive therapy due to miscommunication between patient and nurse.</i> Organizational factor as causal factor of the event.
Other clinical activities	<i>Traumatic placement of urinary bladder catheter in patients with triple antiplatelet therapy, resulting in bladder lavage.</i> Human factors as causal factor of the event.
Other non-procedural activities	<i>None of the preventable adverse events was related to non-procedural activities.</i> N/A
Procedural activities	<i>Substantial renal dysfunction due to contrast given by the coronary angiography in a patient known with acute on chronic renal disease,, in which delayed consultation of the internal medicine department.</i> Patient-related factor as causal factor of the event.
Causal factors	
Human factors	<i>Late detection of subcutaneous edema due to intravenous infusion.</i> Other clinical activities as nature of the event.
Patient-related factors	<i>Delirium post infarction in high-aged patient and immobile by intra-aortic balloon pump without actively taken preventive measures.</i> Other clinical activities as nature of the event.
Technical factors	<i>None of the preventable adverse events was related to non-procedural activities.</i> N/A
Organizational factors	<i>Late detection of massive groin hematoma leading to death.</i> Procedural-related as nature of the event.
Not judgeable	<i>Staphylococcus aureus bacteraemia due to phlebitis of a peripheral intravenous drip of unknown duration.</i> Other clinical activities as nature of the event.

RESULTS

Population

In 2012 and 2013, 879 patients were evaluated and treated for an ACS. As is demonstrated in **Table 2**, patients had a mean age of 64 ± 12 years, the majority was male (71%) and 594 (68%) patients experienced a STEMI. During a median stay of three days (25th–75th percentile: 2 – 4), all patients underwent coronary angiography and 747 (85%) patients were treated by percutaneous coronary intervention.

Adverse events

During 2,999 days of admission, 143 AEs occurred in 116 (13%) patients in which harm was related to care received, rather than to underlying conditions. This resulted in 48 AEs per 1,000 patient days (**Table 3**). **Table 4** illustrates the characteristics of the AEs. The majority resulted in temporary injury (80%), such as a urine tract infection after urinary bladder catheter placement or temporary hypotension after administration of a double dosage of blood pressure medication. However, eight (6%) events were associated with permanent injury, and three (2%) events were associated with serious harm which likely resulted in *death* of the *patient*. Most events were the result of procedural activities (58%) and were related to human factors (55%). Patients with an AE had longer hospital stays compared to patients without an AE (median 4 days (25th–75th percentile: 3 – 6) versus median 3 days (25th–75th percentile: 2 – 4), $p \leq 0.001$). A sub-analysis showed that the patients with one or more missing variables ($n = 161$, 18%) were more often discharged

Table 2: Patient characteristics

	All patients	With an adverse event	Without an adverse event	p-value
	879 patients	116 patients	763 patients	
Age (years)	64 ± 12	69 ± 12	63 ± 12	< 0.001
Female sex	253 (29%)	53 (46%)	200 (26%)	< 0.001
BMI (kg/m ²)	27 ± 4	27 ± 4	27 ± 4	0.976
Infarct characteristics				
Diagnosis				
STEMI	594 (68%)	77 (66%)	517 (68%)	0.425
NSTEMI	135 (15%)	22 (19%)	113 (15%)	
Unstable angina pectoris	150 (17%)	17 (15%)	133 (17%)	
Treated with PCI	747 (85%)	104 (90%)	643 (84%)	0.162
Troponine-T peak (µg/L) (median, IQR)	1.8 (0.3 – 4.8)	2.3 (0.3 – 5.2)	1.7 (0.3 – 4.7)	0.003
CK peak (U/L) (median, IQR)	705(206 – 1665)	910(243 – 1908)	687(200 – 1626)	0.188
Comorbidity				
Hypertension	352 (40%)	60 (52%)	305 (40%)	0.014
Hyperlipidemia	198 (23%)	27 (23%)	175 (23%)	1.000
Diabetes mellitus	115 (13%)	21 (18%)	99 (13%)	0.182
Known coronary artery disease	145 (16%)	23 (20%)	122 (16%)	0.347
Known pulmonary disease	88 (10%)	21 (18%)	68 (9%)	0.004
Renal clearance at admission (10 ml/min per 1.73m ²)	75 ± 23	72 ± 26	75 ± 23	< 0.001

BMI = body-mass index; IQR = interquartile rang; STEMI = ST-elevated myocardial infarction; NSTEMI = non-ST-elevated myocardial infarction; PCI = percutaneous coronary intervention. Missing variables were present in: Troponin-T-peak (14%) and Creatine-Kinase-peak (14), hypertension (3%), hyperlipidemia (3%), diabetes mellitus (2%) and renal clearance (5%).

to another hospital for recovery compared to the patients with no missing variables. No differences were observed on patient characteristics (age, gender, BMI, comorbidities), infarct characteristics (diagnosis, admission duration) or the number of adverse events between the patients with one or more missing variable compared to the patient without missing variable.

Preventable adverse events

A total of 35 (3% of all patients) AEs in 34 patients were judged preventable. This resulted in 12 preventable AEs per 1,000 patient days. Three patients with permanent injury and two patient-deaths were included in this group of patients. The majority was due to procedural activities in the catheterization laboratory (49%) or other clinical activities (29%), and were caused by human factors (63%) (**Table 3&4**). Of note, 10 out of 17 AEs classified as procedural activities were related to the arterial puncture, in which a bleeding or the severity of a bleeding probably could be prevented by optimizing the chain of care and more alert observation after the procedure, or changing the arterial puncture site of the interventional procedure of high risk patients.

Table 3: Occurrence and preventability of adverse events.

879 patients	
Days of observation, total	2,999
Days of observation / per patient	3.4
Length of stay (days) (median, IQR)	3 (2-4)
Number of adverse events	143
Number of preventable adverse events	35
Event risk	
Number of patients with at least one adverse event	116 (13%) (95%-CI: 11%-16%)
Number of patients with at least one preventable adverse event	34 (4%) (95%-CI: 3%-5%)
Event rate	
Adverse event rate	48 per 1,000 patient days
Preventable adverse event rate	12 per 1,000 patient days

Risk estimation

To determine specific parameters correlated to an increased risk for an AE, the univariate regression model shows that age>70 years (OR 2.5 (95%-CI 1.7 – 3.6)), female gender (OR 2.4 (95%-CI 1.6 – 3.5), hypertension (OR 1.6 (95%-CI 1.1 – 2.4)), pulmonary disease (OR 2.3 (95%-CI 1.3 – 3.9), and renal clearance (OR 0.9 (95%-CI 0.9 – 1.0) were predictors of AEs (**Table 5**). The type of infarction (STEMI/NSTEMI) was not significantly associated with the risk for an AE. Using multivariate analysis, patients > 70 years (OR 1.6 (95%-CI 1.0 – 2.6), p=0.042), female sex (OR 3.7 (95%-CI 2.2 – 6.3), p≤0.001) and poor renal function

(OR 0.8 (95%-CI 0.8 – 0.9), $p=0.002$) were significantly associated with an increased risk for AEs.

Table 4: Adverse event characteristics

	143 adverse events	35 preventable adverse event
Consequences of the adverse event		
Possible injury	18 (13%)	1 (3%)
Temporary injury	114 (80%)	29 (83%)
Permanent injury	8 (6%)	3 (9%)
Deceased	3 (2%)	2 (6%)
Nature		
Diagnostic activities	3 (2%)	3 (9%)
Drug-related adverse event	25 (18%)	5 (14%)
Other clinical activities	27 (19%)	10 (29%)
Other non-procedural activities	5 (3%)	0 (0%)
Procedural activities	83 (58%)	17 (49%)
Causal factors		
Human factors	78 (55%)	22 (63%)
Patient-related factors	54 (38%)	10 (29%)
Technical factors	0 (0%)	0 (0%)
Organizational factors	6 (4%)	2 (6%)
Not judgeable	5 (3%)	1 (3%)

Table 5: Correlates of patients with adverse events.

	Univariate regression OR (95%-CI)	p-value	Multivariate regression OR (95%-CI)	p-value
Age > 70 years	2.5 (1.7 – 3.6)	$\leq 0.001^*$	1.6 (1.0 – 2.6)	0.042
Female gender	2.4 (1.6 – 3.5)	$\leq 0.001^*$	3.7 (2.2 – 6.3)	≤ 0.001
BMI (kg/m ²)	1.0 (1.0 – 1.0)	0.976		
Comorbidity				
Hypertension	1.6 (1.1 – 2.4)	0.014*		
Hyperlipidemia	1.0 (0.6 – 1.6)	0.944		
Diabetes mellitus	1.5 (0.9 – 2.5)	0.160		
Known coronary disease	1.3 (0.8 – 2.1)	0.306		
Known pulmonary disease	2.3 (1.3 – 3.9)	0.002*		
Renal clearance (10 L/min per 1.73m ²)	0.9 (0.9 – 1.0)	0.096*	0.8 (0.8 – 0.9)	0.002

* variable was included in multivariate analysis. BMI = body-mass index; Renal clearance is calculated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

Additional evaluation of AE rate by age shows an increase in event rate per age-class, up to a 29% increased risk of experiencing an AE in patients older than 80 years (**Figure 1**). Furthermore, as shown in **Figure 2**, the risk for AEs was highest during the first days of admission (day 0 and 1: 73 AEs, 8% (95%-CI 6.5% – 10.4%) AE risk). A longer admission was also related to an increased risk for AEs (day 10 – 11: 2 AEs, 7% (95%-CI 0.9% – 26.8%) AE risk for the remaining patients). However, the difference is non-significant when compared to the lowest cumulative incidence (day 6 – 7, 1% (95%-CI 0.06% – 14.0%) (p=0.353) (**Figure 2**).

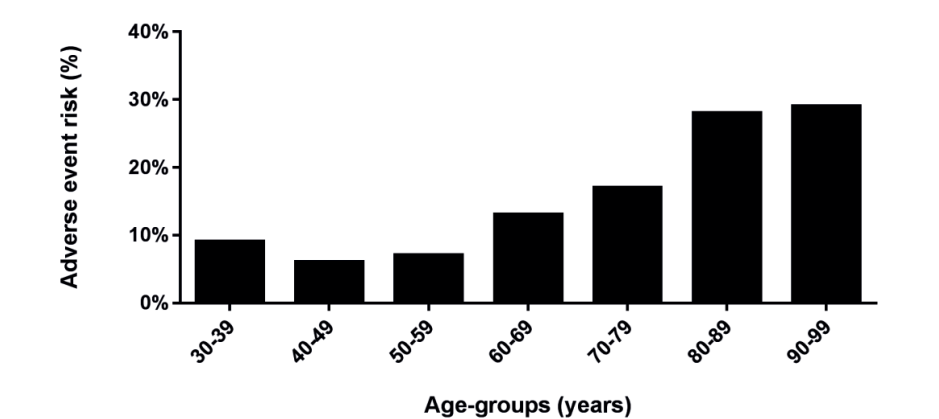


Figure 1: Adverse event risk and age.

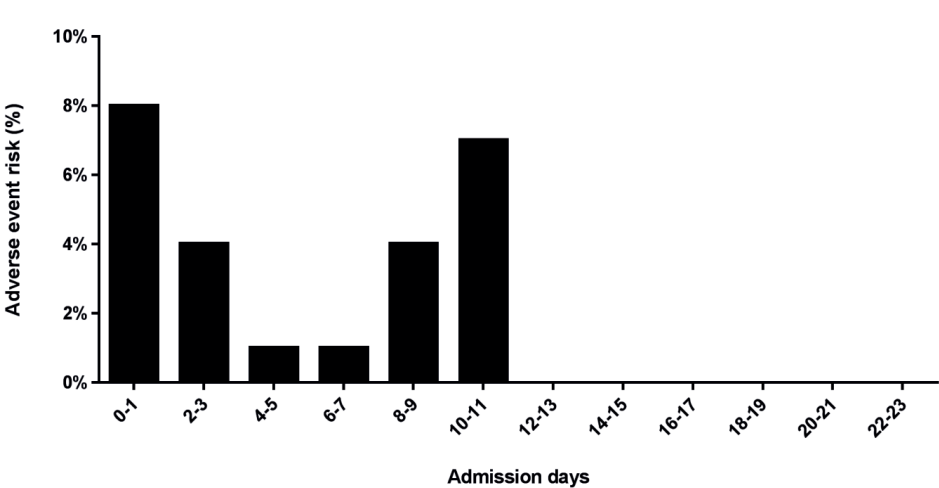


Figure 2: Adverse event risk and admission days.

DISCUSSION

In the current study on the occurrence and the preventability of AEs after treatment of an ACS, the findings can be summarized as follows: (i) 13% of the patients experienced an AE during admission and in 3% of these patients the AEs were preventable; (ii) older age, female sex and poor renal function were associated with an increased risk for AEs; (iii) incidence of AEs was highest during the first days of admission.

Occurrence

After the *"To Err is Human"* publication, an increased awareness to improve patient safety has led to an increasing number of hospital safety programs.²¹ This thesis focused mainly on the (occurrence, severity, nature and causes) of adverse events, because these are more common compared to preventable adverse events and therefore more likely to be actionable on a population level. In the current study in patients treated for an ACS, an AE risk of 13% was observed. This risk is higher compared to previous national data in the Netherlands (5.7-8.0%) while being similar to worldwide registries (2.9-16.6%) which examined the risk of AEs in the general hospital population.^{3-11, 22} To our knowledge, no previous record review study has been performed in ACS patients. When compared to the national data, a higher event rate in the current study could be caused by the fact that treatment of an ACS happens in an acute setting and is characterized by time-pressure decisions, patient complexity and acuity, and high risk interventions. A recent Swedish study, which also focussed on a specific population (orthopaedic patients), detected a higher AE rate (15%) compared to other local and nationwide Swedish studies.²³ Furthermore, risk factors for AEs in ACS patients have not been identified in prior studies. The current study reveals different factors influencing the risk for AEs: significantly more AEs occurred in patients with an older age, female sex, and a poor renal function. The higher risk of AE in female patients was unexpected. Although females are more likely to present with atypical symptoms of ischemia and show higher short-term mortality after acute coronary syndromes, clinical evidence is lacking on the reason why females are more susceptible to AEs.²⁴⁻²⁶

Preventability

An AE was defined preventable when the performance of the practitioner or health care organization falls short of the expected level of competence. In the present study, 3% of all patients experienced a preventable adverse event, which is lower when compared to other studies (28 – 70%).^{3, 22, 27} Zegers et al. reported in a sub-analysis of cardiology departments in The Netherlands an AE rate of 4.9% in 1,165 admissions in which 33% was preventable.²² Previously, McDonald suggested that the proportion of preventable AEs, particularly preventable deaths, is overestimated because of inadequate consideration of other factors

such as severity and complexity of patient disease.²⁸ In this study, the method and the specified population provided the opportunity to take into account the acute setting and complexity of the patients.

The majority of patients with a preventable AE recovered without permanent disability. However, two patients died as a result of the preventable AE and these cases deserve careful consideration. As stated before by Brennan et al., death associated with medical error is not preventable if death would have occurred even in the absence of error.¹⁰ Hayward and Hoger found that many preventable deaths occurred at the end of life or in critically ill patients in whom death was the most likely outcome either during the hospitalization or in the coming months, regardless of the care received.²⁹ It is difficult to judge what the expected risk of death is, or would have been in the absence of an AE. Both cases were critically ill patients whose death was considered imminent. Still, their deaths could perhaps have been prevented if physicians had paid more attention to the complaints of the patient, if they would have performed more diagnostics, or if the physicians were more restrained in performing a therapeutic intervention considering the high-risk anatomy of the patient. Although the number of preventable AEs is low, the department tries to learn from these events by discussing these cases in the monthly departmental Mortality and Morbidity Review Committee Meeting. The goal hereby is to create a continuous learning cycle which may improve the patient safety for all ACS patients.

The relation between admission duration and adverse events

The highest risk for a patient to experience an AE is during the first days of the admission (8% of all admitted patients). More specifically, the majority of the AEs were related to the interventional procedure (58%), which takes place during the first days (day 0&1). This study showed that the occurrence of an AE could cause a prolonged admission, which is also reported in previous studies.³⁰⁻³² Conversely, a prolonged admission may expose in-hospital patients to the occurrence of an AE. For example, a longer admission leads to a higher exposure of peripheral infusion catheters and therefore to a higher phlebitis and AE rate³³. Likewise, serious in-hospital falls were independently correlated with an increased length of stay up to the time of fall³⁴. Apparently in these patients, during a prolonged hospital stay (at day 10-11), a second, new peak in risk for AEs is observed. However, these results are based on a small number of events and are therefore non-significant. Hence, it is difficult to attribute a causal relationship between a prolonged admission and the occurrence of AEs in patients based on this study.

Future implications

Since these results are based on a single centre, this requires caution in generalizing these findings to other centres. However, this study emphasizes that research on patient safety

on a departmental level is important, and the value of safety as a core value in an organization should be embedded in clinical care. Besides, adverse events lead to a prolongation of the hospital admission and impose a large financial burden.^{31, 35, 36} Considering the fact that human factors were often the cause of (preventable) AEs, it will be of interest for future research to specify these human factors in more detail, for example diagnostic errors due to a lack of knowledge, lack of coordination at discharge or lack of communication and education of the patient.

Additionally, to ensure that medical errors are reliably reported and analyses at a departmental level, a proper safety culture is warranted. A proper safety culture entails that reporting a human error is blame-free and that attention is given to optimizing the communication and teamwork between care providers.²¹ Furthermore, the ultimate goal is to improve patient safety using real-time monitoring of process-deviations and AEs or, even better, to predict which patients are at risk for AEs (like female gender or a decreased kidney function) in order to prevent harm

Limitations

Some limitations have to be addressed. This study had a retrospective patient record review design and shares the limitations of all retrospective analyses. For example, overestimation in determining the causation and preventability of an event is possible when knowing its outcome. A prospective approach can augment the assessment of contributing factors of an AE.^{37, 38} However, this is laborious and costly. Although judgements about the presence of an AEs are difficult and never fully objective, retrospective patient record review studies are currently one of the best methods available to assess incidence of AEs and discover latent errors.³⁹ Unfortunately, it was not possible to take into account all potential risk factors (e.g. thrombocytopenia, anaemia, femoral access vs. radial access) and care aspects (e.g. time of presentation of AMI (off-hours versus regular hours), subtypes of causal factors) which could potentially explain an increased risk of having an AE. Hence, more research is warranted concerning these risk factors, for example to disentangle the relation observed between gender and a higher risk for AE.

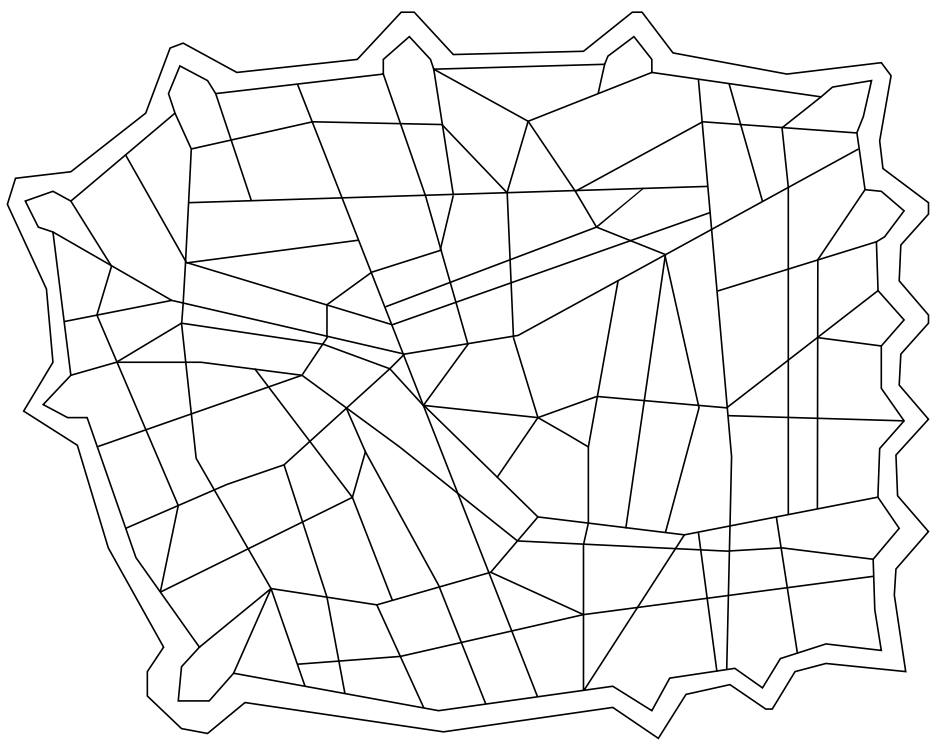
CONCLUSION

The results of this study imply that harm due to health care is a serious problem in ACS patients. During admission for an ACS, 13% of patients experienced an AE of which 24% (3% of all patients) was preventable. Patients who are older, female or with a decreased renal function are at increased risk.

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Chapter 4

A focus on female gender in the treatment of acute coronary syndrome patients; determining differences in the type, nature and preventability of adverse event rates by means of medical record review.

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Submitted

ABSTRACT:

BACKGROUND: Numerous studies reported that female patients treated for an acute coronary syndrome have poorer cardiovascular outcomes and receive less optimal treatment compared to male patients.

AIM: The aim of this study was to assess whether there is a gender disparity in the nature, occurrence and preventability of harm in patients with an acute coronary syndrome.

METHODS: A structured retrospective patient record review was performed to screen for adverse events during admission for the treatment of a suspicion of acute coronary syndrome warranting coronary angiography. An adverse event was defined as an unintended injury resulting in disability at time of discharge, prolonged hospital stay or death, that was caused by health care management rather than a patient's underlying disease.

RESULTS: In total, 879 patients (age 64 (SD 12) years, 71% male) were included. Female patients were slightly older, were less often diagnosed with a STEMI and were less often treated by percutaneous coronary intervention. Of the 626 male patients, 10% (95%-CI: 7%–12%) experienced an adverse event whereas in the group of 253 female patients, 21% (95%-CI: 16%–26%) patients experienced an adverse event ($p \leq 0.001$). No differences were found in the nature of the AEs between male and female patients ($p = 0.360$), however the causal factors of the adverse events were significantly different between male and female patients (adverse event $p = 0.043$). Female gender remained a significant predictor for adverse events after adjustment for lifestyle factors, medication, comorbidities and treatment characteristics (OR=2.4, $p < 0.001$).

CONCLUSION: Women experience more adverse events compared to men. Gender is an independent predictor of adverse events after adjustment for lifestyle factors, medication, comorbidity and treatment characteristics.

INTRODUCTION

Adverse events are a major cause of mortality and morbidity among hospitalized patients. Therefore, patient safety is a serious health care issue and research on the incidence, preventability and causes of adverse events is receiving growing attention since the *To Err is Human* report in 1999.¹ Herein, adverse events are defined as medical injuries resulting in disability or death *due to health care management*, rather than attributable to the underlying disease process. Previous studies reported adverse events rates of 2.9 % to 16.6% based on all types of clinical admissions.²⁻¹³ A recent study which focused on adverse events in patients treated for acute coronary syndrome showed that among patients admitted for the treatment of an acute coronary syndrome, 13% experienced an adverse event. Female patients, elderly and patients with an impaired renal function were at increased risk for an adverse event.¹⁴ This poorer outcome in female patients, which has been demonstrated in terms of mortality and complications in previous studies, seems to be at least partly explained by sex differences in baseline characteristics, biomarkers, symptom presentation, prognosis and management of acute coronary syndrome.¹⁵⁻²⁴ Female patients with a myocardial infarction are older and have more comorbidities (such as hypertension and diabetes mellitus), and therefore have a higher risk of adverse cardiovascular outcomes.^{18,23,25} Furthermore, accumulating evidence suggests that also female specific risk factors can influence the onset and outcome of myocardial infarction.¹⁹

In contrary to the vast amount of knowledge regarding the risk factors and differences in health outcomes (i.e. mortality and complications as bleeding) between male and female myocardial patients there is a scarcity of knowledge regarding potential differences in the underlying causes that lead to these adverse events. Hence, this study adds to the current body of knowledge by examining differences in causal factors, nature and the consequences of adverse events between male and female patients treated for an acute coronary syndrome.

METHODS

Patient population

All patients with a suspicion of acute coronary syndrome warranting coronary angiography, who were evaluated and treated according to a strict evidence-based protocol (the MISSION! Protocol) are included.²⁶⁻²⁸ Since the goal of this study was to examine differences in the occurrence, nature and causal factors of experiencing an adverse event in patients with a suspicion of acute coronary syndrome, irrespective of the final treatment that was given, no differentiation was made between patients that did receive or did not receive

a coronary angiography after diagnosis. For the current study, patients were evaluated for the occurrence and preventability of adverse events during the in-hospital program. All patients treated in 2012 and 2013 were extracted from the electronic patient record system (EPD-Vision, LUMC, Leiden The Netherlands) by selecting the diagnose coding of a diagnosis-treatment-combination for unstable angina (UA) (11.203), ST-segment elevation myocardial infarction (STEMI) (11.204) and non-ST-segment elevation myocardial infarction (NSTEMI) (11.205).

Evaluation of adverse event

Through a structured medical record review, patients were assessed for the occurrence of adverse events by trained independent physician reviewers. The method is based on the Harvard Medical Practice Study.¹² A comprehensive description of the method is described in a previous study.²⁹ Summarized, the first phase focuses on identifying process deviations during the admission. A process deviation was defined as every operation or treatment that differed from the MISSION!-protocol²⁸, such as additional procedures (a pacemaker implantation or second PCI procedure), prescription of extra medication other than described in the protocol (use of anti-arrhythmics, anti-coagulation, inotropics or diuretics) or omission of a procedure (no diagnostics performed). If a process deviation was present, the medical record was transferred to a second phase which involved an assessment on whether the event resulted in harm to the patient. Patient harm was defined as any disadvantage for the patient that resulted in prolonged or strengthened treatment, temporary or permanent (physical and/or mental) impairment or death. Furthermore, it was rated whether patient harm was caused by medical care (and therefore an adverse event) and if so, whether it was potentially preventable (and therefore caused by an error). In case of doubt the expert panel, consisting of experienced cardiologists, was consulted. When more than one adverse event occurred in a patient, both were registered. Adverse events were classified by severity (leading to possible injury, temporary injury, permanent injury or death), nature (e.g. as a consequence of taken medication, procedural activities, diagnostic activities or other clinical activities) and causal factors (technical, human, organisational or patient-related factors) were noted.³⁰ Only the first (preventable) event was taken into account when comparing differences in the frequency of nature and causal factors.

Evaluation of gender differences

To examine the potential gender differences in the treatment, number of adverse events and type of adverse events of patients with acute coronary syndrome various factors were taken into account. Information on risk factors and comorbidities was collected, including on hypertension (defined as blood pressure $\geq 140/90$ mmHg or previous pharmacological treatment), hyperlipidaemia (defined as total cholesterol ≥ 190 mg/dl or previous pharmacological treatment), smoking, a diagnose of diabetes mellitus (insulin

and non-insulin-dependent), history of coronary artery disease or previous percutaneous coronary intervention, history of pulmonary diseases and renal clearance at admission. Renal clearance was measured by calculating the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.³¹ The comorbidity score at baseline was calculated using an abbreviated Charlson Comorbidity Index (CCI) with the following comorbid conditions: myocardial infarction, cerebrovascular disease, chronic obstructive pulmonary disease, diabetes mellitus, peripheral vascular disease, liver disease, renal failure and any malignancy.³² The abbreviated CCI was computed in accordance with the original CCI in which a weight of 2 was assigned to renal failure and any malignancy, and a weight of 1 to the other comorbid conditions. Because age is a risk factor for mortality independent of the presence of comorbid conditions, the score was adjusted by adding one point to the score for each decade of life over the age of 50 at time of study entry.³³ Moreover, medication use known at admission and discharge was noted for aspirin-species, P2Y12-inhibitors, statins, beta-blockers and angiotensin converting enzyme inhibitor or angiotensin-2-antagonist (ACE/AT2-inhibitors).

Furthermore, infarct characteristics and treatment were collected, such as prior diagnosis (STEMI, NSTEMI and UA), percutaneous treatment, peak Troponin-T and creatine kinase (CK). STEMI was defined in the presence of symptoms of angina lasting longer than 30 minutes with typical electrocardiographic changes (ST-segment elevation ≥ 0.2 mV in ≥ 2 contiguous leads in V1 through V3, or ≥ 0.1 mV in other leads, or presumed new left bundle branch block.³⁴ In addition, treatment variables as symptom-to-needle-time, diagnosis-to-needle-time and door-to-needle-time were noted. Symptom-to-needle time was defined as the time between the onset of symptoms and first needle puncture during the procedure in the catheterization laboratory. Diagnosis-to-needle time was defined as the time between the first diagnostic ECG, usually the ambulance triage ECG, and the time of the needle puncture.

Statistical analysis

Adverse event rates were calculated by taking the proportion of patients with at least one adverse event and the number of adverse events per 1,000 patient days. For the calculation of the 95% confidence interval for event rates, a Poisson distribution of the observed number of events was presumed. Continuous variables were presented as means with standard deviations or medians with 25th and 75th percentiles. Dichotomous variables were presented as numbers and percentages. Demographic and clinical characteristics were stratified by male and female gender. To examine gender differences in experiencing an adverse event, demographic variables, risk factors, comorbidities and medication use known at baseline were compared by means of T-tests, Mann-Whitney U tests, or chi-squared-test, where appropriate. Logistic regression was used to examine lifestyle factors, comorbidities, medi-

cation at admission, treatment factors as influencing the gender differences in experiencing an adverse event during admission. Due to missing values on symptom-to-needle time (~13%), Troponin-T-peak (~14%) and medication at admission (~4%), multiple imputation was performed by using Predictive Mean Matching (Markov Chain Monte Carlo, 100 imputations). Predictive mean matching is similar to the regression method except that for each missing value, it imputes a value randomly from a set of observed values whose predicted values are closest to the predicted value for the missing value from the simulated regression model.³⁵ Subsequently, the imputation database was used to perform a logistic regression. Gender was entered in the hierarchical regression analyses using the *enter* method (Model 1). Subsequently, socio-demographic variables (age, body-mass index and smoking), medication (aspirin, P2Y12-inhibitor, statin, beta-blocker and ACE/AT2-inhibitor) were added to the analyses thereby creating Model 2 and Model 3, respectively. To determine if treatment comorbidities or treatment characteristics were predictive of adverse event during admission, Charlson Comorbidity Index, Diagnosis, PCI, symptom-to-needle-time (divided in four groups by quartiles) and Troponin-T (for each gender divided in four groups by quartiles), were added to the logistic regression model (Model 4 and 5). In Model 4, age was excluded because it was already incorporated in the Charlson Comorbidity Index. The explained variance of Model 1 to Model 5 were estimated using block entry of the variable groups and were calculated based on a method for combining R square values from imputed data sets.³⁶

Furthermore, of each variable, an odds ratio with standard error and a p-value was calculated. All analyses were performed with IBM SPSS Statistics for Windows, Version 23.0 (SPSS, Armonk, NY, USA) and a p-value < 0.05 was considered statistically significant.

Ethical considerations

The institutional ethical committee of Leiden University Medical Center gave a declaration of “medical-ethical permittance not necessary” for this retrospective records study (reference number P15.133). Data was analysed anonymously.

RESULTS

Population

In total, 879 patients (mean age of 64 (SD = 12) years) were evaluated and treated for an acute coronary syndrome. The majority of the patients was male (71%, n = 626) and 594 (68%) patients experienced a STEMI. During a median stay of three days (25th – 75th percentile: 2 – 4), all patients underwent coronary angiography and 747 (85%) patients were treated by PCI. Further demographic, clinical and medication characteristics are shown in **Table 1**.

Table 1: Patient characteristics

	All patients	Male	Female	p-value
	N = 879	N = 626	N = 253	
Age (years)	64 (SD 12)	63 (SD 12)	65 (SD 13)	0.070
BMI (kg/m ²)	27 (SD 4)	27 (SD 4)	26 (SD 5)	0.202
Comorbidities				
Charlson Comorbidity Index	2.7 (SD 2.1)	2.7 (SD 2.1)	2.7 (SD 2.0)	0.560
Current smoker	326 (37%)	243 (39%)	97 (38%)	0.927
Medication use at home				
Aspirin-specie	203 (23%)	138 (22%)	65 (26%)	0.278
P2Y12-inhibitor	51 (6%)	30 (5%)	21 (8%)	0.071
Statin	256 (29%)	180 (29%)	78 (31%)	0.616
Beta-blocker	225 (26%)	140 (22%)	85 (34%)	0.001
ACE- or AT2-inhibitor	243 (28%)	162 (26%)	81 (32%)	0.074
Admission characteristics				
Length of stay (days) (median, IQR)	3 (2 – 4)	2 (3 – 4)	3 (2 – 5)	0.055
Diagnosis				0.006
STEMI	594 (68%)	445 (71%)	149 (59%)	
NSTEMI	135 (15%)	87 (14%)	48 (19%)	
Unstable angina	150 (17%)	94 (15%)	56 (22%)	
Percutaneous coronary intervention	747 (85%)	541 (86%)	206 (81%)	0.060
Symptom-to-needle time (minutes) (median, IQR)	228 (124 – 669)	202 (117 – 556)	320 (149 – 1,045)	0.001
Diagnosis-to-needle time (minutes) (median, IQR)	70 (55 – 192)	69 (54 – 148)	75 (56 – 265)	0.035
Troponin-T-peak (µg/L) (median, IQR)	1.8 (0.3 – 4.8)	2.1 (0.4 – 5.0)	1.1 (0.2 – 3.6)	0.001
CK-peak (U/L) (median, IQR)	705(206 1,665)	882(239 1,723)	488(151 – 1,414)	≤ 0.001
Medication at discharge				
Aspirin-specie	834 (95%)	592 (95%)	243 (96%)	0.493
P2Y12-inhibitor	789 (90%)	567 (91%)	222 (88%)	0.214
Statin	824 (94%)	590 (94%)	233 (92%)	0.276
Beta-blocker	756 (86%)	550 (88%)	206 (81%)	0.016
ACE- or AT2-inhibitor	774 (88%)	561 (90%)	212 (84%)	0.020

SD = standard deviation; BMI = body-mass index; IQR = interquartile rang; STEMI = ST-segment elevation myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; CK = Creatine kinase.

Gender variety

Gender differences in baseline characteristics are shown in **Table 1**. Female patients were slightly older (65 (SD = 13) years versus 63 (SD = 12) years, $p = 0.070$), were less often diagnosed with a STEMI (71% versus 59%, $p = 0.006$), had a lower Troponin-T-peak (female 1.1 (IQR 0.2 – 3.6) vs male 2.1 (IQR 0.4 – 5.0) ($p = 0.001$) and lower CK peak (female 488

(IQR 151 – 1,414) vs male 882 (IQR 239 – 1,723) ($p \leq 0.001$)). Moreover, female patients had more risk factors compared to male patients, such as hypertension (female 51% versus male 38%, $p \leq 0.001$). Subsequently, differences were found in the treatment of female patients. Female patients were less often treated by PCI (female 81% versus male 86%, $p = 0.060$), were less often treated with a beta-blocker ($p = 0.016$) and ACE- or AT2-inhibitor ($p = 0.020$) at discharge, and also the time from first symptom-to-treatment (females 320 minutes (IQR 149 – 1,045) vs males 202 minutes (IQR 117 – 556) ($p = 0.001$)) and diagnosis-to-treatment (females 75 (56 – 265) vs males 69 (IQR 54 – 148) ($p = 0.035$)) was longer compared to male patients.

Within the group of STEMI patients, the symptom-to-needle time was consistently longer in female patients (166 minutes (IQR 155 – 328) compared to male patients (150 minutes (IQR 102 – 249) ($p = 0.019$)). No differences were observed in diagnosis-to-needle time ((females 62 minutes (IQR 50 – 77) vs males 62 minutes (IQR 51 – 75) ($p = 0.775$)) and PCI-treatment (females 97% versus males 95%, $p = 0.387$).

Adverse events

During 2,999 days of observation, a total of 143 adverse events were observed in 116 patients. In the group of 626 male patients, 63 (10% (95%-CI: 7% – 12%)) patients experienced an adverse event, while in the group of 253 female patients, 53 (21% (95%-CI: 16% – 26%)) patients experienced an adverse event ($p \leq 0.001$). Similarly, a significant difference was seen in the number of patients with at least one preventable adverse event: 6% among female patients (95%-CI: 3% – 9%) compared to 3% among male patients (95%-CI: 2% – 4%) (≤ 0.001). (Table 2) The difference in the frequency of adverse events between female and male patients was also observed when the same analysis was performed on the group of STEMI patients ($n = 594$) (females 19% versus males 11%, $p = 0.006$). In both female (13 events) and male patients (9 events), adverse events were mainly related to bleeding complications.

When examining the nature and causes of all first events in 116 patients, it appears that 72% of all events in the group of female patients were related to procedural activities, compared to 56% in the group of male patients ($p = 0.360$). This difference was also found in the preventable adverse events (male 28% vs female 75% due to procedural activities, $p = 0.042$). The causal factors of (preventable) adverse events were also significantly different between male and female patients (adverse event $p = 0.043$, preventable adverse event $p = 0.021$). Human factors were the primary cause of (preventable) adverse events in female patients (female AE: 68% and female preventable AE: 75% respectively). Human factors (male AE: 51%, male preventable AE: 50%) and patient-related factors (male AE: 43%, male preventable AE: 50%) were found as the primary causes of the (preventable) adverse

Table 2: Occurrence and preventability of adverse events.

	All patients	Male	Female	p-value
	N = 879	N = 626	N = 253	
Days of observation, total	2,999	2,060	939	
Days of observation / per patient	3.4	3.3	3.7	
Number of adverse events	143	78	65	
Number of preventable adverse events	35	18	17	
Event risk				
Number of patients with at least one adverse event	116 (13%) (95%-CI: 11–16%)	63 (10%) (95%-CI: 7– 12%)	53 (21%) (95%-CI: 16– 26%)	≤ 0.001
Number of patients with at least one preventable adverse event	34 (4%) (95%-CI: 3– 5%)	18 (3%) (95%-CI: 2– 4%)	16 (6%) (95%-CI: 3– 9%)	0.021
Event rate				
Adverse event rate	48 per 1,000 patient days	38 per 1,000 patient days	69 per 1,000 patient days	
Preventable adverse event rate	12 per 1,000 patient days	9 per 1,000 patient days	18 per 1,000 patient days	

events in male patients.(Table 3) Focussing on preventable adverse events with a human factor, no explicit differences between male and female patients were found. Examples of human factors related to preventable adverse events were delayed percutaneous interventions in an NSTEMI patient despite evolving electrocardiographic changes during the weekends (male gender), traumatic placement of urinary bladder catheter in patients with triple anti platelet therapy resulting in bladder lavage (male gender), and late detection of subcutaneous edema due to intravenous infusion (female gender), late detection and consultation of an NSTEMI at a pulmonary department (female gender).

Risk factors by gender

Between patients with and without an adverse event, stratified by gender (male AE = 63, male non-AE = 563, female AE = 53, female non-AE = 200) data were compared on the same variables as used in Table 1. Differences between patients with and without an adverse event were found in both gender groups in age (male AE versus male non-AE, $p = 0.001$; female AE vs female non-AE, $p = 0.002$) and Charlson Comorbidity Index (male AE versus male non-AE, $p \leq 0.001$; female AE vs female non-AE, $p = 0.009$). Female gender with an adverse event were less often smokers (21% vs 43%, $p = 0.004$) compared to female patients without an adverse event. No differences were observed in the type of diagnosis (p -values all above 0.05) in male and female patients. However, symptom-to-needle time was significantly longer in female patients with an adverse event (440 minutes (233 – 1,790) compared to females without an adverse event 317 minutes (144 – 936), $p =$

Table 3: Adverse event characteristics

All adverse events	Adverse event		p-value	All preventable adverse event		p-value
	Male	Female		Male	Female	
N = 116	N = 63	N = 53	0.308	N = 34	N = 16	0.109
Consequences of the adverse event						
Possible injury	15 (13%)	8 (15%)		1 (3%)	0 (0%)	1 (6%)
Temporary injury	92 (79%)	41 (77%)		28 (82%)	15 (83%)	13 (81%)
Permanent injury	7 (6%)	2 (4%)		3 (9%)	3 (17%)	0 (0%)
Deceased	2 (2%)	2 (4%)		2 (6%)	0 (0%)	2 (13%)
Nature						
Diagnostic activities	2 (2%)	1 (2%)	0.360	2 (6%)	1 (6%)	1 (6%)
Drug-related adverse event	19 (16%)	14 (22%)		5 (15%)	4 (22%)	1 (6%)
Other clinical activities	20 (17%)	12 (19%)		10 (29%)	8 (44%)	2 (13%)
Other non-procedural activities	2 (2%)	1 (2%)		0 (0%)	0 (0%)	0 (0%)
Procedural activities	73 (63%)	35 (56%)		17 (50%)	5 (28%)	12 (75%)
Causal factors						
Human factors	68 (59%)	32 (51%)	0.043	21 (62%)	9 (50%)	12 (75%)
Patient-related factors	38 (33%)	27 (43%)		10 (29%)	9 (50%)	1 (6%)
Technical factors	0 (0%)	0 (0%)		0 (0%)	0 (0%)	0 (0%)
Organizational factors	5 (4%)	1 (2%)		2 (6%)	0 (0%)	2 (13%)
Not judgeable	5 (4%)	3 (5%)		1 (3%)	0 (0%)	1 (6%)

0.048). Furthermore, male patients with an adverse event were more often treated by PCI (95% vs 85%, $p = 0.032$) and P2Y12 inhibitors (98% vs 90%, $p = 0.033$).

Multivariate analyses

The odds of experiencing an adverse event are explained by gender for 3.6% - 4.8%. Gender remained a significant predictor for adverse events after adjustment for lifestyle factors, medication, comorbidities and treatment characteristics (OR1 = 2.4, SE = 0.2; OR2 = 2.3, 0.2; OR3 = 2.3, SE = 0.2, OR4 = 2.5, SE = 0.2, OR5 = 2.4, SE = 0.2; all p -values ≤ 0.001). (Table 4) The explained variance of the lifestyle and socio-demographic factors (minus age), medication use prior to admission, and comorbidity in Model 4 was 1,7%, 1,7%, and 4,1%, respectively. The explained variance of the lifestyle factors and socio-demographic factors (including age), medication use at home, and treatment variations in Model 5 was 6%, 1,4%, and 2,1%, respectively. In addition to gender, age (Model 2, Model 3 and Model 5 all values OR = 1.0, SE 0.0, $P \leq 0.001$), the degree of comorbidity (OR4 = 1.3, SE 0.1, $p \leq 0.001$) and the symptom-to-needle time (OR5 = 1.3, SE = 0.3, $p = 0.036$) remained significant predictors for adverse events. (Table 4)

DISCUSSION

In this study on gender disparities in the treatment, number of adverse events and type of adverse events in patients with acute coronary syndrome, the findings can be summarized as follows: (i) Women experience more adverse events compared to men (female patients (21%) vs. males (10%)); (ii) Women have a more unfavourable baseline risk profile (due to age and comorbidities) and are less often treated according to clinical guidelines, which may partly explain the higher odds of having an adverse event; (iii) Adverse events in women are more often related to human factors compared to men; (iv) Gender is an independent predictor of adverse events after adjustment for lifestyle factors, medication, comorbidities and treatment characteristics.

The prevalence of adverse events observed in this study was higher compared to previous national registries and similar to worldwide studies.^{2-13,37} The majority of these adverse events were related to bleeding complications. In cardiovascular literature, no previous study focused on examining patient harm caused specifically by health care management. However, previous studies did consistently find a higher risk of bleeding complications in female patients, which could be associated with higher mortality rates.^{16,22,24,38,39} Unfortunately, the interaction between gender and baseline characteristics and antithrombotic treatment, that can increase or decrease the risk of having a bleeding event, remains poorly understood. It seems that in women acute myocardial infarction is more frequently caused

Table 4: Multivariate analysis

	Model 1			Model 2			Model 3			Model 4			Model 5		
	OR	SE	p-value	OR	SE	p-value	OR	SE	p-value	OR	SE	p-value	OR	SE	p-value
Gender	R2 = 0.036			R2 = 0.036			R2 = 0.036			R2 = 0.035			R2 = 0.036		
Gender	2.368	0.204	≤ 0.001	2.270	0.209	≤ 0.001	2.287	0.213	≤ 0.001	2.471	0.215	≤ 0.001	2.362	0.217	≤ 0.001
Lifestyle & socio-demographic factors				R2 = 0.096			R2 = 0.096			R2 = 0.052			R2 = 0.096		
Age				1.043	0.009	≤ 0.001	1.043	0.010	≤ 0.001				1.040	0.010	≤ 0.001
BMI				1.029	0.025	0.250	1.025	0.026	0.326	1.014	0.026	0.593	1.028	0.026	0.287
Smoking				0.733	0.243	0.201	0.757	0.248	0.262	0.703	0.243	0.148	0.695	0.252	0.147
Medication at home				R2 = 0.110			R2 = 0.110			R2 = 0.069			R2 = 0.110		
Aspirin				0.540	0.313	0.049	0.483	0.318	0.022	0.526	0.319	0.044			
P2Y12-inhibitor				1.533	0.421	0.310	1.467	0.425	0.368	1.513	0.435	0.341			
Statin				1.321	0.277	0.316	1.195	0.283	0.528	1.377	0.282	0.256			
Beta-blocker				0.905	0.278	0.726	0.860	0.287	0.600	0.965	0.288	0.903			
ACE/AT2-inhibitor				1.296	0.252	0.303	1.226	0.258	0.429	1.221	0.256	0.434			
Comorbidities				R2 = 0.110			R2 = 0.110			R2 = 0.110			R2 = 0.131		
Charlson Comorbidity Index										1.279	0.055	≤ 0.001			
Treatment characteristics													R2 = 0.131		
Diagnosis STEMI / NSTEMI													1.372	0.339	0.350
Troponin-T-Peak													1.109	0.122	0.395
Percutaneous coronary intervention													1.751	0.356	0.116
Symptom-To-Needle Time (minutes)													1.326	0.282	0.036

BMI = body-mass index; ACE/AT2-inhibitor = angiotensin converting enzyme or angiotensine-2-inhibitor; STEMI = ST-segment elevation myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction;

by plaque erosion, and women tend to suffer more from non-obstructive cardiac disease and coronary microvascular dysfunction compared to men.^{40,41} Hormonal differences, like the endogenous oestrogen levels in the premenopausal phase of the vascular endothelium, have been described as a protective factor for acute coronary syndrome in women,^{17,42} but women do show a higher platelet reactivity compared to men.^{43,44}

Although a gender-disparity in baseline biological characteristics exists, studies appear to show a largely comparable efficacy of antithrombotic treatment for acute coronary syndrome.¹⁶ Hochholzer showed in the TRITON-TIMI-38 trial that complications in men were mainly related to gastrointestinal bleeding, whereas those in women were mainly related to the vascular access site of bleeding.⁴⁵ Moreover, female gender was a predictor for serious bleeding of any cause.⁴⁵

As confirmed in other registries, demographic and lifestyle risk profile at admission differ between female and male patients. Also in this study, female patients were older and had more comorbidities, such as hypertension. Other registries also showed that diabetes, congestive heart failure, renal insufficiency and cerebrovascular disease were more prevalent in female gender.^{39,46-49} Surprisingly, in our study a better renal function was observed in females compared to males. Our findings also indicate that female patients were less often treated according to the guidelines (lower number of PCI procedures and longer symptom-to-needle time), which seems consistent with the “risk-treatment paradox”.²⁵ The “risk-treatment paradox” is a situation in which patients at high risk for adverse events receive less-intensive treatment than do patients at lower risk.⁵⁰ This is in concordance to other studies showing that women were more often treated with medical therapy alone compared to men, had a delay in PCI times and were less likely to receive discharge medication according to guidelines or to medication continue after one year follow-up.^{48,51-54} Poon et al. showed that the “risk-treatment paradox” could be the result of an underappreciation of the increased risk associated with female gender.⁵⁴

Most predictors of adverse events, such as demographic factors (age), lifestyle factors, comorbidities and treatment patterns were partly associated with the odds of having adverse events in our study. Especially gender seems to be an important independent predictor for experiencing an adverse event. Also in studies focusing on young women with coronary artery disease after PCI, an increased risk of major adverse cardiovascular events (target vessel and target lesion failure) is observed.⁵⁵ When focussing on the events itself, the majority of the events in females were caused by human factors, whereas events in males were caused by medication and human factors. Other factors, such as communication and symptom presentation by female patients could play a role in identifying an adverse event to prevent further harm. Often, women present without chest pain or discomfort when

having an acute coronary syndrome.²⁰ Moreover, women are less aware of having an acute coronary syndrome and underestimate their risk by attributing acute coronary syndrome mainly as a 'male problem'.⁵⁶ Women also showed a delay in seeking care, based on the time between the first symptoms and having the first medical contact.^{20,51,57}

Limitations

This study is one of the first studies which focusses on gender differences in patient's harm caused by health care management after treatment for an acute coronary syndrome. However, some limitations need to be addressed. This study shares the limitations of a retrospective study. In addition, the chance of experiencing an adverse event can dependent on numerous factors, which could not all be taken into account in this study. Furthermore, judging whether an adverse event is preventable is subjective to potential hindsight bias. Despite this limitation, retrospective medical record review studies are currently one of the best methods available to assess incidence of AEs and discover latent errors.⁵⁸

Future perspectives

In the future, a greater awareness of sex-based differences regarding the treatment and symptom presentation of acute coronary syndrome might be important in preventing adverse events. An increased focus on unravelling the causes of specific adverse events (i.e. bleeding) and whether this is caused by the "risk-treatment paradox" or gender itself seems important, as well as a greater focus on gender-specific treatment during the education of physicians. Furthermore, clinical guidelines should place a greater emphasis on the gender-difference in the treatment of cardiovascular disease, and the pharmaceutical industry and scientific researchers should be encouraged to initiate clinical trials with an equal representation of male and female patients.

CONCLUSION

Gender is an independent predictor of adverse events after adjustment for lifestyle factors, medication, comorbidities and treatment characteristics. More research is needed to disentangle the underlying causes which increase the risk for adverse events in women compared to men.

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Part Two

Quality of Care on a National Level



Chapter 5

Nationwide claims data validated for quality assessments in acute myocardial infarction in the Netherlands.

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ABSTRACT:

INTRODUCTION: Since health insurance is obliged in the Netherlands, the centrally registered medical claims data might pose a unique opportunity to evaluate quality of (cardiac) care on a national level without additional collection of data. However, validation of these claims data has not yet been assessed.

DESIGN: Retrospective cohort study.

METHODS: National claims data ('national registry') were compared with data, collected by patient records reviews in four representative hospitals ('validation registry'). In both registries, we extracted the national diagnosis codes for ST-segment elevation myocardial infarction and non-ST-segment elevation myocardial infarction of 2012 and 2013. Additionally, data on medication use at one year after acute myocardial infarction (AMI) was extracted from the Pharmacy Information System and also validated by local patient records reviews. The data were compared at three stages: 1) validation of diagnosis and treatment coding; 2) validation of the hospital where follow-up has taken place; 3) validation of follow-up medical treatment after 365 days.

RESULTS: In total, 3980 patients ('national registry') and 4014 patients ('validation registry') were compared at baseline. After one-year follow-up, 2776 and 2701 patients, respectively, were evaluated. Baseline characteristics, diagnosis and individual medication were comparable between the two registries. Of all 52,672 AMI patients in the Netherlands in 2012 and 2013, 81% used aspirin, 76% used P2Y12 inhibitors, 85% used statins, 82% used beta-blockers and 74% angiotensin converting enzyme inhibitors/angiotensin II antagonists. Optimal medical treatment was achieved in 49% of the patients with AMI.

CONCLUSION: Nationwide routinely collected claims data in patients with an acute myocardial infarction are highly accurate. This offers an opportunity for use in quality assessments of cardiac care.

INTRODUCTION

An acute myocardial infarction (AMI) is the most frequent cause of death in the western world.¹ Numerous studies have shown the beneficial effects of medication following AMI, resulting in increased survival.²⁻⁷ In modern medicine the assessment of quality of care has become increasingly important, especially measurements focussing on patient-relevant outcomes such as mortality and patient experience.⁸ Health care professionals have a responsibility to monitor their performances and share these results. However, registration of clinical parameters is laborious and time-consuming, which results in less time for actual patient care.⁹

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Internationally, claim and clinical databases are explored as a source for quality assessments.^{10, 11} The added value of claims databases is the automatic data collection on an ongoing basis, allowing us to follow patients over a longer period of time and cover large populations.¹²⁻¹⁴ However, nationwide coverage is scarce. The centrally registered claims data of health care companies in the Netherlands might pose a unique opportunity to evaluate quality of cardiac care on a national level. As all inhabitants of the Netherlands are obliged to have health insurance, almost all inhabitants (99,8%) are registered in a central database (excluding military personnel and prisoners). However, the validity of these claims data has not been assessed.

In the current study, national claims data will be validated for its use in the assessment of quality of care on a national scale. For the validation of claims data, medical treatment in the first year following AMI will be assessed as a first quality indicator.

METHODS

Validation method

To assess validity of national claims data, four representative hospitals are assessed by comparing claims data of each hospital ('national registry') to local data, which is obtained by local patient record reviews ('validation registry').

National registry

In the Netherlands, all reimbursements of the Dutch hospitals are processed by insurance companies and registered by a national diagnosis coding system. These are centrally registered and collected in the Dutch Hospital Information Systems. Furthermore, information on prescribed medication was extracted from the Dutch Pharmacy Information System. For the current analysis, we selected all patients admitted in 2012 and 2013 for an ST-segment

elevation myocardial infarction (STEMI) (coded as 0320.11.204) or a non-ST-segment elevation myocardial infarction (NSTEMI) (coded as 0320.11.205). The age, gender and initial treatment (either percutaneous coronary intervention (PCI) or no PCI) of all patients were registered.

The hospital where the first follow-up code was registered was considered the hospital where follow-up had taken place and therefore responsible for medical treatment. If no follow-up code was registered, patients with a PCI were allocated to the centre in which the PCI was performed and patients without a PCI were allocated to the hospital with the first STEMI or NSTEMI code.

For one year following the index event, mortality and the use of the following medication was noted: aspirin (acetylsalicylic acid and carbasalate calcium), P2Y12 inhibitor, statin, beta-blocker, angiotensin converting enzyme (ACE) inhibitor or angiotensin II antagonist (AT2 antagonist). Optimal medical treatment was defined as the usage of these five medications. Furthermore, the use of a vitamin K antagonist (VKA) or novel oral anticoagulant (NOAC) was noted as a potential cause for non-usage of aspirin.

Medication use

Medication use was defined by the registered anatomical therapeutic chemical (ATC) code and the defined daily dose (DDD). The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults, composed by the World Health Organisation Collaborating Centre for Drug Statistics Methodology.¹⁵ It is a unit of measurement and does not necessarily reflect the recommended or prescribed daily dose. The complete list of the DDD per medication is shown in **Table 1**. The use of pharmacy records is validated in previous studies.¹⁶

National cohort

Baseline data and pharmacological treatment after one-year follow-up of all patients with AMI in the Netherlands in 2012 and 2013 were assessed.

Validation registry

In the four selected hospitals (an academic PCI centre, two peripheral PCI centres and a non-PCI centre), all variables extracted from the national claims database, were collected for validation through patient records reviews. Patients with foreign health insurance were excluded, since these patients were not included in the national analysis. The data from the national registry and validation registry databases were compared at three stages (**Fig. 1**).

Table 1: Definition of medication use after 365 days

Medication	ATC Code	DDD 365 days
Aspirin	B01AC06 (acetylsalicylic acid) or B01AC08 (carbasalate calcium)	180 DDD
P2Y12 inhibitor	B01AC04 (clopidogrel), B01AC22 (prasugrel) and B01AC24 (ticagrelor)	180 DDD
Statin	C10AAxx (all HMG CoA reductase inhibitors)	180 DDD
Beta-blocker	C07xxxx (all beta-blocking agents and combinations)	45 DDD
ACE/AT2 antagonist	C09A, C09B and C09C (including combinations)	120 DDD
Vitamin K antagonist	B01AA04 (phenprocoumon) and B01AA07 (acenocoumarol)	60 DDD
Novel oral anticoagulant	B01AE07(dabigatran etexilate), B01AF01 (rivaroxaban) and B01AF02 (apixaban)	180 DDD

ACE angiotensin converting enzyme, AT2 angiotensin II ATC anatomical therapeutic chemical, DDD defined daily dose HMG CoA hydroxymethyl-glutaryl coenzyme.

To increase the algorithm's sensitivity for detecting medication usage, a threshold of 45 to 180 DDD was used.

1) Validation of diagnosis and treatment coding at first admission

In every hospital, the patient population was selected by using the hospital's local claims registration database to find all admitted patients with the similar national diagnosis codes for STEMI and NSTEMI. In patients with multiple diagnosis codes within the study period, the first admission code was used for the analysis. All codes were checked for the final diagnosis at discharge in which STEMI is defined as ST-elevation in ≥ 2 contiguous leads with ≥ 0.1 mV in all leads other than leads V2-V3 and a typical rise and/or fall of cardiac biomarkers.¹⁷ An NSTEMI diagnosis is defined by clinical symptoms suggestive for acute ischaemia, with or without ST-segment depression or T-wave and presence of cardiac biomarkers.¹⁸

2) Validation of the hospital where follow-up has taken place

In the validation hospitals, all patient records were screened to assess where follow-up was performed. Patients whose follow-up was performed in another hospital were excluded from follow-up analyses. Additionally, in the non-PCI centre, patients could have been referred from another hospital where the initial AMI was registered, in which case these patients were included for follow-up analysis. Finally, all patients deceased within one year after their first admission were excluded from the follow-up population, similar to the national database, since one-year medication use could not be assessed.

3) Validation of pharmacological treatment during one-year follow-up

All remaining patient records were reviewed for medication use.

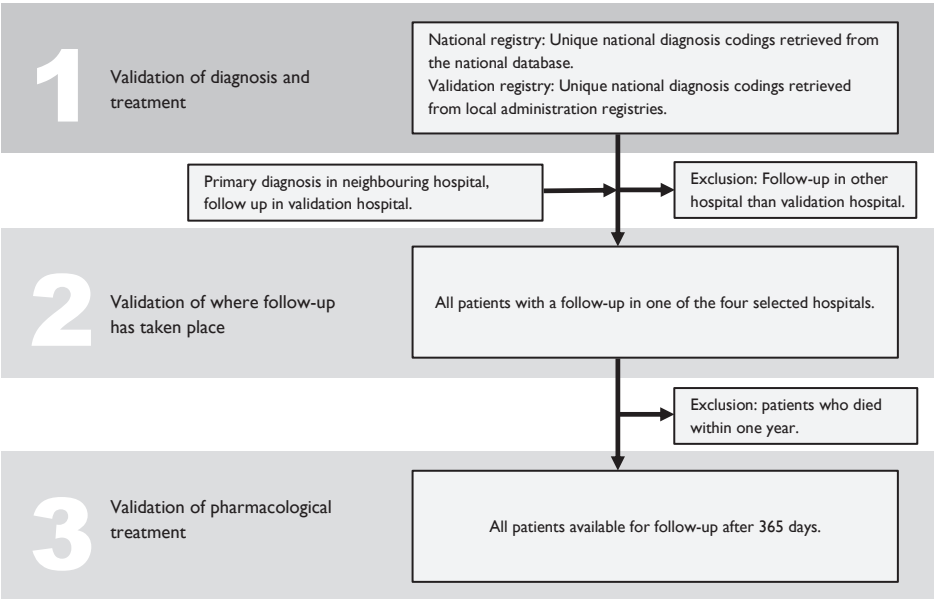


Figure 1: Data from the national registry and validation registry databases are compared at three stages.

Statistical analysis

The data are compared as absolute numbers and as a proportion of the total population. A 95% confidence interval (CI) was calculated with a population proportion formula and indirect comparisons were made by chi-square test between the national registry and validation registry. A *p*-value above 0.05 was considered comparable. Furthermore, a direct comparison of the diagnosis coding in the local database with the final diagnosis at discharge was made.

Ethical approval

For the use of anonymised national data, permission of national insurance companies was provided. In case of the local patient records review, the Leiden University Medical Center, in its capacity as coordinating centre of this retrospective study, gave a statement of “medical ethics approval not required” (reference number P15.265). The other participating hospitals also formally consented to participate in accordance with their local medical ethics committee.

RESULTS

1) Validation of diagnosis and treatment

Of all 59,534 admissions for AMI in the Netherlands in 2012 and 2013, 3980 (7%) patients were registered in one of the four validation hospitals according to the claim database. Half of the diagnosis codes were for STEMI (51%) (95% CI 49%-53%), 68% (95% CI 67%-70%) was treated with PCI, mean age was 66 ± 13 years and 68% (95% CI 67%-70%) were male.

With patient records reviews in the four hospitals, 4014 patients were identified. Similar to the national registry, 51% of the patients had a STEMI code (95% CI 49%-53%), 69% (95% CI 67%-70%) was treated with PCI, mean age was 66 ± 13 and 69% (95% CI 67%-70%) were male (**Table 2**). For the direct validation of the diagnosis codes, the final diagnosis at discharge was correlated with the first diagnosis coding. Due to transfers after treatment, a reliable judgement for final diagnosis was not possible in 254 (6%) patients. Of all remaining 1,977 STEMI codes, 88% was coded correctly as STEMI. Of all 1,738 NSTEMI codes, 93% was coded correctly as NSTEMI.

Table 2: Patient characteristics

	National registry	Validation registry	Difference	National cohort
	N = 3,980	N = 4,014		N = 59,534
Age (yrs)	66 ± 13	66 ± 13		67 ± 13
Male gender	2,726 (68%)	2,756 (69%)	1%	39,545 (66%)
Deceased < 180 days	313 (8%)	292 (7%)	1%	5,471 (9%)
Deceased < 365 days	388 (10%)	346 (9%)	1%	6,862 (12%)
Final diagnosis				
STEMI	2,028 (51%)	2,048 (51%)	0%	25,768 (43%)
NSTEMI	1,952 (49%)	1,966 (49%)	0%	33,766 (57%)
Treated with PCI	2,700 (68%)	2,754 (69%)	1%	31,632 (53%)

STEMI = ST-segment elevation myocardial infarction, NSTEMI non-ST-segment elevation myocardial infarction, PCI percutaneous coronary intervention

2) Validation of the hospital where follow-up has taken place

To validate the national algorithm of the location where follow-up had taken place, all patients with outpatient follow-up in another centre were excluded. In the national registry, 3106 patients had their first follow-up code after their AMI was registered in one of the four selected hospitals. Three hundred and thirty patients died within one year and were excluded, resulting in a follow-up population of 2,776 patients.

In the validation registry of 4014 patients, 1157 patients received follow-up in another hospital, 146 patients were followed in one of the hospitals although the first admission of AMI was registered elsewhere, and 302 patients died during the first year, resulting in a validated follow-up population of 2701 patients.

3) Validation of pharmacological treatment

Analysis of 2,776 patients in the national registry showed an aspirin use of 81% (95% CI 79%-82%), P2Y12 inhibitor use of 80% (95% CI 78%-81%), statin use of 91% (95% CI 90%-92%), beta-blocker use of 86% (95% CI 85%-87%), ACE inhibitor/AT2 antagonist use of 80% (95% CI 78%-81%), VKA use of 17% (95% CI 15%-18%) and NOAC use of 1% (95% CI 0%-1%) (**Table 3**).

In the validation registry, one-year medication data were available in 1,986 patients, showing comparable rates between the two registries (**Table 3**).

Table 3: Pharmacological treatment during one year follow-up

	National registry	Validation registry	Difference	National cohort
	N = 2,776	N = 2,701		N = 52,672
Patients with data available		N = 1,986		
Aspirin	2,246 (81%)	1,689 (85%)	4%*	42,717 (81%)
P2Y12 inhibitor	2,207 (80%)	1,565 (79%)	1%	39,990 (76%)
Statin	2,525 (91%)	1,847 (93%)	2%	44,548 (85%)
Beta-blocker	2,386 (86%)	1,607 (81%)	5%*	43,189 (82%)
ACE inhibitor/AT2 antagonist	2,213 (80%)	1,656 (83%)	3%	38,795 (74%)
Vitamin K antagonist	465 (17%)	293 (15%)	2%	8,669 (16%)
Novel oral anticoagulant	14 (1%)	13 (1%)	0%	184 (0%)
Optimal medical treatment	1,665 (60%)	1,087 (55%)	5%*	25,615 (49%)
With aspirin	1,439 (52%)	959 (48%)	4%	22,311 (42%)
With VKA or NOAC	226 (8%)	128 (6%)	2%	3,304 (6%)
At least 4 out of 5	2,217 (80%)	1,589 (80%)	0%	38,795 (74%)
At least 3 out of 5	2,545 (92%)	1,863 (94%)	2%	46,885 (89%)

ACE inhibitor = Angiotensin converting enzyme inhibitor, AT2 = antagonist angiotensin II antagonist, VKA = vitamin K antagonist, NOAC = novel oral anticoagulant

Optimal medical treatment is defined as the use of a combination of aspirin-specie and/or vitamin K antagonist or novel oral anticoagulant, P2Y12 inhibitor, statin, beta-blocker and ACE inhibitor. The replacement of VKA or NOAC is not included in the combined measurements in which patients use at least three or four out of five medications.

* P-value > 0.05 for comparison between the national registry and validation registry.

National cohort

Of all 59,534 patients (mean age 67 ± 13 years, 66% male), 6,862 (12%) patients died during one-year follow-up (**Table 2**). The remaining 52,672 patients showed an aspirin use of 81%, P2Y12 inhibitor use of 76%, statin use of 85%, beta-blocker use of 82%, ACE inhibitor/AT2 antagonist use of 73% (**Table 3**).

DISCUSSION

In this study on validation of claims data, the findings can be summarised as follows: (i) the two registries show comparable results for PCI-treatment, diagnosis and medical treatment in AMI patients, making it possible to use claims data for quality assessments on a national scale; (ii) medical adherence one year after AMI in the Netherlands is at an acceptable level.

Claims data and quality assessment

With the growing importance of quality assessment and efficient data collection, routinely collected claims data are being used more frequently and studied for cardiac outcome measurements. Benefits of claims databases are the automatic and continuous data acquisition which make it less laborious for health care professional to gather health care outcome measurements. Claims data have the advantage of nationwide coverage, depend less on voluntary hospital participation and for chain of care evaluation, including connection with external datasets. However, claims data are collected for billing purposes rather than for research. Therefore, it requires validation of data accuracy. Data accuracy is particularly important when using claims data as a quality indicator and when comparing medical centres. As previously shown in the UK, the current study demonstrates a sufficient accuracy of nationwide-used diagnostic, procedural and medical treatment codes with chart review.¹⁹ Other studies on comparisons of claims data with clinical registries show various results.²⁰⁻²² This is due to differences in medical specialisation, study purpose and database quality. This analysis composes a large sample size (7% of all Dutch AMI patients) and data quality is verified in various stages. Altogether, the use of nationwide claims data offer an efficient approach in quality measurement on a national scale. However, claims data contain limited detailed clinical information, which must be taken into account. Adjustment for patient characteristics and case mix is possible up to a certain level, but requires additional evaluation.^{22, 23}

Medication compliance following myocardial infarction

Several large trials have shown the beneficial effects of medication on patient outcome.²⁻⁷ Therefore, medication poses a robust indicator for quality of care following an AMI.²⁴

Previous studies focussing on medication at discharge show a substantial guideline adherence in patients with AMI (65%–69% were prescribed all 5 indicated drugs).^{25, 26} Additionally, a recent European guideline evaluation by the EUROASPIRE IV Study Group showed comparable secondary prevention rates at a median follow-up time of 16 months after the myocardial infarction: 94% antiplatelets, 86% statins, 83% beta-blockers and 75% ACE inhibitors/AT2 antagonists.²⁷ Another study from the Netherlands evaluates secondary prevention during long-term follow-up with usage of a similar patient linkage system containing drug-dispensing records from community pharmacies and hospitalised patients and shows an improvement in medication compliance over time (from 1999 till 2007).²⁸ When comparing these results with the current study, an additional improvement in medication adherence over time can be observed, suggesting an increased focus on adequate medication prescription after AMI. Approximately half of the currently studied patients do not receive all five indicated drugs one year after AMI. The measured suboptimal adherence of all five indicated drugs is partly physician driven (the drugs are not prescribed, whether or not on purpose) and can be partly patient driven (the patient does not want the medication or is intolerant).^{4, 18, 29} In the guidelines of the European Society of Cardiology, American Heart Association and American College of Cardiology, beta-blocker and ACE inhibitor/AT2 antagonist use is indicated for patients with left ventricular dysfunction (Class 1, level A) and recommended if not contra-indicated in the remaining group.^{4, 18, 29} A combined measurement of the five indicated drugs might have its limitations as a quality indicator and therefore requests careful interpretation. Comparison per type of medication poses a more robust indicator for the assessment of quality of care.

Future implications

National claims data offer a range of possibilities for automated and nationwide quality assessments without additional work for professionals, resulting in more time for actual patient care. Furthermore, national claims data serve as an opportunity in the evaluation of the patient's chain of care. Future research should focus on the development of additional quality indicators and on the connection between currently available databases, such as primary care databases to assess primary care follow-up, or nursery care databases to assess functional status. In the Netherlands, claims data serve as an additional measurement, alongside the National Heart Registry (NHR).³⁰ The NHR could function as a national clinical database with more detailed clinical information. National claims data could be used to check the number in the clinical databases. In the long run, when the field of cardiac professionals is ready, cost effective analysis is possible. A development that can already be seen in the field of surgery, with the Dutch Institute for clinical auditing (DICA) and claims data.³¹ All in all, this depends on new laws concerning privacy and the will of politicians, hospitals and clinical professionals.

Limitations

Some limitations should be addressed. Firstly, differences in adherence between local and national databases may also be caused by different adherence measuring methods; national databases are based on pharmacy fulfilment prescription and local databases are based on self-reporting of the patient, deducted from a chart review. This discrepancy between providing and fulfilment of the prescription is not studied and therefore a small difference between the two registries is in accordance with clinical practice and doesn't relate to data quality. Secondly, patients were lost to follow-up in the validation registry. Reasons were a physician- or patient-driven conservative approach because of the patient's terminal disease or high age. Patients who were lost to follow-up may be the patients that used less medication and therefore could probably cause a selection bias of the validation registry.

CONCLUSION

Nationwide routinely collected medical claims data in patients with AMI are accurate. This offers an opportunity for use in quality assessments of cardiac care.

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Chapter 6

Age and Gender Differences in Medical Adherence after Myocardial Infarction: Women do not receive optimal treatment: The Netherlands Claims Database.

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ABSTRACT

BACKGROUND: Following myocardial infarction, medication is, besides lifestyle interventions, the cornerstone treatment to improve survival and minimize the occurrence of new cardiovascular events. Still, data on nationwide medication adherence are scarce. This study assesses medical adherence during one year following myocardial infarction, stratifying per type of infarct, age and gender.

METHODS: In the Netherlands, all inhabitants are by law obliged to have health insurance and all claims data are centrally registered. In 2012 and 2013, all national diagnosis-codings of ST-Elevation myocardial infarction (STEMI) and Non-ST-Elevation myocardial infarction (NSTEMI) were acquired. Furthermore, information on retrieved medication was extracted from the Dutch Pharmacy Information System. Twelve months after discharge, the retrieved medication at the pharmacy of each pharmacological therapy (aspirin-species, P2Y12-inhibitor, statin, beta-blocker, ACE/AT2-inhibitor, vitamin-K antagonists or novel oral anticoagulant) were analysed.

RESULTS: In total, 59,534 patients (67 ± 13 years, 39,545 (66%) male, 57% NSTEMI) were included of whom 52,672 (88%) patients were analysed for one-year medical adherence. STEMI patients more often achieved optimal medical adherence than NSTEMI patients (60% vs. 40%, $p \leq 0.001$). In both STEMI and NSTEMI, use of all five indicated drugs was higher in male patients compared to female (STEMI male 61% vs. female 57%, $p \leq 0.001$; NSTEMI male 43% vs. female 37%, $p \leq 0.001$). With increasing age, a gradual decrease was observed in the use of aspirin, P2Y12-inhibitors and statins.

CONCLUSION: Age and gender differences existed in medical adherence after myocardial infarction. Medical adherence was lower in women, young patients and elderly patients, specifically in NSTEMI patients.

INTRODUCTION

Cardiovascular disease, mostly due to coronary artery disease, is the most frequent cause of death worldwide with 17.5 million cases in 2012.¹ Following acute myocardial infarction, optimal medical therapy is, besides lifestyle interventions, the cornerstone treatment to increase survival, improve cardiac function and minimize the occurrence of new cardiovascular events.^{2, 3} The European Society of Cardiology (ESC) and American Heart Association /American College of Cardiology guidelines recommend to prescribe the 'Golden Five', which is a combination of two types of platelet inhibitors (aspirin-specie and a P2Y12-inhibitor), a statin, a beta-blocker and an angiotensin-converting enzyme (ACE) inhibitor or angiotensin-II (AT2) inhibitor. Specifically, beta-blocker and ACE/AT2-inhibitor use is indicated for patients with LV dysfunction (Class I, level A) and recommended if not contra-indicated in the remaining group (Class IIa, level A).⁴⁻⁶ With the increasing incidence of acute myocardial infarction and the improved prognosis, the group of patients needing lifelong medication continues to expand.⁷ In 2016, the EUROASPIRE investigators reported an adherence rate of cardio-protective medication in surviving patients among 24 European countries ranging from 75% - 94% after 6 months.⁸ Data was retrieved by reviewing medical records and patient interviews. However, until now, no complete data are available on nationwide medication adherence during prolonged follow-up.

In the Netherlands, it is mandatory for all inhabitants to have health insurance. All claims data are registered in the central claims database of the insurance companies in the Netherlands.⁹ This database contains diagnose codings and demographic parameters of all patients. Additionally, all medication claims data are registered in Dutch Pharmacy Information System. This national database serves as a unique opportunity to assess medication adherence following acute myocardial infarction, stratified by diagnose, age and gender.

METHODS

In the Netherlands, all reimbursements of hospitalised patients are coded by diagnosis and treatment according to a national financial coding system. Hospital claims are sent to the patient's insurance company and subsequently collected in the central database of the insurance companies in The Netherlands, the Dutch Hospital Care Information System. Furthermore, information on prescriptions which are retrieved by the patient and claimed by the pharmacist, can be extracted from the Dutch Pharmacy Information System. These two databases can link on an individual patient level by the data manager of the national insurance companies (Vektis B.V., Zeist, The Netherlands).

Patients

All patients with a diagnose code for a ST-segment Elevation Myocardial Infarction (STEMI) (code 0320.11.204) or a non-ST-segment Elevation Myocardial Infarction (NSTEMI) (code 0320.11.205) in 2012 and 2013 were selected. The following characteristics were retrieved: age, gender, treatment by percutaneous coronary intervention during initial hospitalisation, and mortality during 12 months after first diagnose registration. Mortality data are retrieved from the Hospital Care Information System in which deregistration from the insurance company with given reason 'dead' is recorded. For the analysis on medical adherence during long-term follow-up, patients who died during twelve months follow-up were excluded, since these patients could not have used medication during the entire period. The remaining patients were considered the study population.

Medication

Twelve months after discharge of the initial event, the fulfilled prescriptions of each pharmacological therapy (aspirin (acetylsalicylic acid and carbasalate calcium), P2Y12-inhibitor, statin, beta-blocker, ACE/AT2-inhibitor, vitamin-K antagonists (VKA) or Novel Oral Anticoagulant (NOAC)) were collected. Medicine usage was defined by using the then prevailing Anatomical Therapeutic Chemical (ATC)-code and the Defined Daily Dose (DDD). DDD is composed by the World Health Organisation Collaborating Centre for Drug Statistics Methodology and is the assumed average maintenance dose per day for a drug used for its main indication in adults. For each pharmacological therapy the minimum number of used tablets per day above a dosage threshold was used. The DDD-definition per medication is validated in previous studies and in this cohort.¹⁰⁻¹² The use of national claims data was validated by comparing national claims data of four representative hospitals to local data, which is obtained by local patient records review. The overall accuracy was above 95%.¹²

An aspirin included the ATC-codes B01AC06 (acetylsalicylic acid) or B01AC08 (carbasalate calcium), P2Y12-inhibitor by ATC-codes B01AC04 (clopidogrel), B01AC22 (prasugrel) and B01AC24 (ticagrelor), statins by ATC-codes C10AAxx (all HMG CoA reductase inhibitors), beta-blocker by ATC-codes C07xxxx (all beta-blocking agents and combinations), ACE/AT2-inhibitors by ATC-codes C09A, C09B and C09C (including combinations), Vitamin-K-antagonists by ATC-codes B01AA04 (phenprocoumon) and B01AA07 (acenocoumarol), and Novel Oral Anticoagulants by ATC-codes B01AE07 (dabigatran etexilate), B01AF01 (rivaroxaban) and B01AF02 (apixaban).

Optimal medical adherence was defined by the usage of aspirin, P2Y12-inhibitor, statin, beta-blocker, ACE/AT2-inhibitor. Additionally, replacement of aspirin with a VKA or NOAC was also considered optimal medical adherence, according to the current international

guidelines.^{4, 5} Furthermore, the use of at least three or four out of five medications was analysed.

Statistical analyses

Data will be presented as absolute numbers and as a proportion of the total population, including numerator and denominator. Comparisons were done by chi-square test. A p-value below 0.05 was considered significantly different. Data was analysed using SAS® Version 9.3 (SAS Institute, Cary NC).

Ethical considerations

Informed consent was not acquired because personal identifiable data was encrypted and anonymised. For the use of anonymised national data, permission of the national insurance companies was provided. The Leiden University Medical Center gave permission and a declaration of “medical-ethical permittance not necessary” at the start of the study (reference number P15.265).

RESULTS

Patients

In 2012 and 2013, a total of 59,534 patients were diagnosed with an acute myocardial infarction in the Netherlands. Patients had a mean age of 67 ± 13 years and 66% was male. The majority was diagnosed with a NSTEMI (57%, mean age of 69 ± 13 years, 64% male), 43% with a STEMI (64% male mean age of 64 ± 13 years, 70% male). After one year, 6,862 (12%) patients died (2,986 STEMI; 3,876 NSTEMI) which resulted in a follow-up population of 52,672 patients. Of these patients, 2,061 patients were diagnosed with both STEMI and NSTEMI during the study period, resulting in a total follow-up population of 23,655 STEMI and 31,078 NSTEMI admissions in 52,672 unique patients during 2012 and 2013.

Table 1: Baseline characteristics.

	Total	STEMI	NSTEMI
Total number of patients	N = 59,534	N = 25,630	N = 33,904
Age (yrs.)	67 ± 13	64 ± 13	69 ± 13
Male gender	39,545 (66%)	17,879 (70%)	21,666 (64%)
Treated with percutaneous coronary intervention	31,638 (53%)	20,016 (78%)	11,622 (34%)

STEMI = ST-segment Elevation Myocardial Infarction; NSTEMI = Non-ST-segment Elevation Myocardial Infarction.

Percutaneous coronary intervention

Of all AMI-patients, 31,638 were treated with a PCI (57% of all male, 46% of all female patients, $p \leq 0.001$). In STEMI-patients, 14,308 (80%) male patients received more often a PCI compared to 5,708 (74%) of the female patients ($p \leq 0.001$). Also in NSTEMI-patient, women were less often treated with PCI (male 38% vs female 28%, $p \leq 0.001$).

Medical adherence

Of all STEMI-patients, 20,355 (86%) used an aspirin, 20,297 (86%) a P2Y12-inhibitor, 21,193 (90%) a statin, 19,975 (84%) a beta-blocker, 18,435 (78%) an ACE/AT2-inhibitor during the year following STEMI. 14,167 (60%) patients received optimal medical adherence (use of all five recommended medications or replacement of aspirin with VKA or NOAC). As is shown in **Table 2**, NSTEMI patients were significantly less often treated with the combination of recommended medication, resulting in only 12,500 (40%) patients being treated optimally.

Table 2: Medical adherence in STEMI and NSTEMI patients, during one year after acute myocardial infarction.

	AMI	STEMI	NSTEMI	p-value
	N = 52,672*	N = 23,655	N = 31,078	
Aspirin	42,717 (81%)	20,355 (86%)	21,789 (70%)	≤ 0.001
P2Y12-inhibitor	39,990 (76%)	20,297 (86%)	20,134 (65%)	≤ 0.001
Statin	44,548 (85%)	21,193 (90%)	22,858 (74%)	≤ 0.001
Beta-blocker	43,189 (82%)	19,975 (84%)	22,079 (71%)	≤ 0.001
ACE-inhibitor/AT2-inhibitor	38,795 (74%)	18,435 (78%)	19,584 (63%)	≤ 0.001
Vitamin K antagonist	8,669 (16%)	3,122 (13%)	4,594 (15%)	≤ 0.001
Novel oral anticoagulant	184 (0%)	44 (0%)	95 (0%)	0.006
Optimal medical adherence	25,615 (49%)	14,167 (60%)	12,500 (40%)	≤ 0.001
With aspirin	22,311 (42%)	12,534 (53%)	10,815 (35%)	≤ 0.001
With VKA or NOAC	3,304 (6%)	1,633 (7%)	1,685 (5%)	≤ 0.001
At least 4 out of 5	38,795 (74%)	19,527 (83%)	19,609 (63%)	≤ 0.001
At least 3 out of 5	46,885 (89%)	22,130 (94%)	24,082 (77%)	≤ 0.001

ACE-inhibitor = angiotensin-converting-enzyme-inhibitor, AT2-inhibitor = angiotensin-2-inhibitor, VKA = vitamin-K antagonist, NOAC = novel oral anticoagulant. Optimal medical adherence is defined as the use of a combination of aspirin (or replaced by VKA or NOAC), P2Y12-inhibitor, statin, beta-blocker and ACE/AT2-inhibitor.

* Unique patients when combining STEMI and NSTEMI patients.

Differences in gender

In general, medical adherence was higher in male STEMI and NSTEMI patients (**Table 3**). As shown in **Figure 1 & 2 & Table 3**, differences between male and female patients were less evident in STEMI patients than in NSTEMI patients. Following STEMI, female patients

were less often treated with aspirin (84% vs. 87%, $p \leq 0.001$), statins (86% vs. 91%, $p \leq 0.001$) and ACE/AT2-inhibitor (75% vs. 79%, $p \leq 0.001$). Optimal medical adherence was achieved in 57% of all female patients compared to 61% in male patients ($p \leq 0.001$) (**Figure 1**). Following NSTEMI, 37% of female patients and 43% of male patients was treated optimally ($p \leq 0.001$) (**Figure 1**). Differences between female and male patients

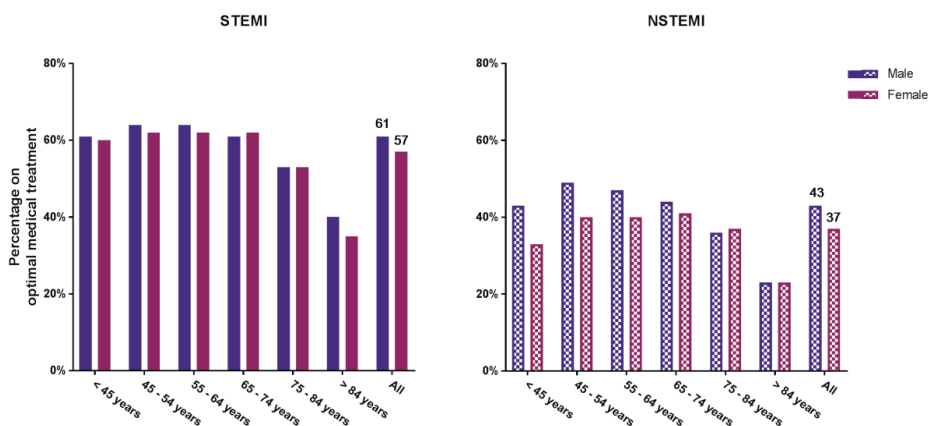


Figure 1: Optimal medical adherence

Table 3: Medical adherence in female and male patients, during one year after acute myocardial infarction.

	Male Gender	Female Gender	p-value
	N = 35,456	N = 17,216	
Aspirin	29,423 (83%)	13,294 (77%)	≤ 0.001
P2Y12-inhibitor	27,566 (78%)	12,424 (72%)	≤ 0.001
Statin	30,958 (87%)	13,590 (79%)	≤ 0.001
Beta-blocker	29,179 (82%)	14,010 (81%)	0.010
ACE-inhibitor/AT2-inhibitor	26,559 (75%)	12,236 (71%)	≤ 0.001
Vitamin K antagonist	5,597 (16%)	3,072 (18%)	≤ 0.001
Novel oral anticoagulant	1150 (0%)	69 (0%)	0.163
Optimal medical adherence	17,988 (51%)	7,627 (44%)	≤ 0.001
With aspirin	15,728 (44%)	6,583 (38%)	≤ 0.001
With VKA or NOAC	2,260 (6%)	1,044 (6%)	0.169
At least 4 out of 5	27,077 (76%)	11,718 (68%)	≤ 0.001
At least 3 out of 5	32,261 (91%)	14,624 (85%)	≤ 0.001

ACE-inhibitor = angiotensin-converting-enzyme-inhibitor, AT2-inhibitor = angiotensin-2-inhibitor, VKA = vitamin-K antagonist, NOAC = novel oral anticoagulant.

Optimal medical adherence is defined as the use of a combination of aspirin (or replaced by VKA or NOAC), P2Y12-inhibitor, statin, beta-blocker and ACE/AT2-inhibitor.

were most outspoken in the use of aspirin (73% vs. 80%, $p \leq 0.001$), P2Y12-inhibitors (65% vs. 71%, $p \leq 0.001$) and statins (75% vs. 84%, $p \leq 0.001$).

Differences in age

As is shown in **Figure 1**, optimal medical adherence decreases with higher age. In STEMI patients, 37% of the patients older than 84 years achieved medical adherence, compared to 60% in all STEMI patients ($p \leq 0.001$). In NSTEMI patients, 23% of patients older than 84 years of age are treated optimally, compared to 41% of all NSTEMI patients ($p \leq 0.001$).

As is shown in **Figure 2 and 3**, in both STEMI and NSTEMI patients, for all five recommended drugs, optimal adherence was observed in the middle aged categories (45 – 74 years). In STEMI patients, with increasing age, a gradual decrease is observed in the use of aspirin, P2Y12-inhibitors and statins. These results can be noted in NSTEMI patients as well although, in contrast, the use of beta-blockers increased with higher age.

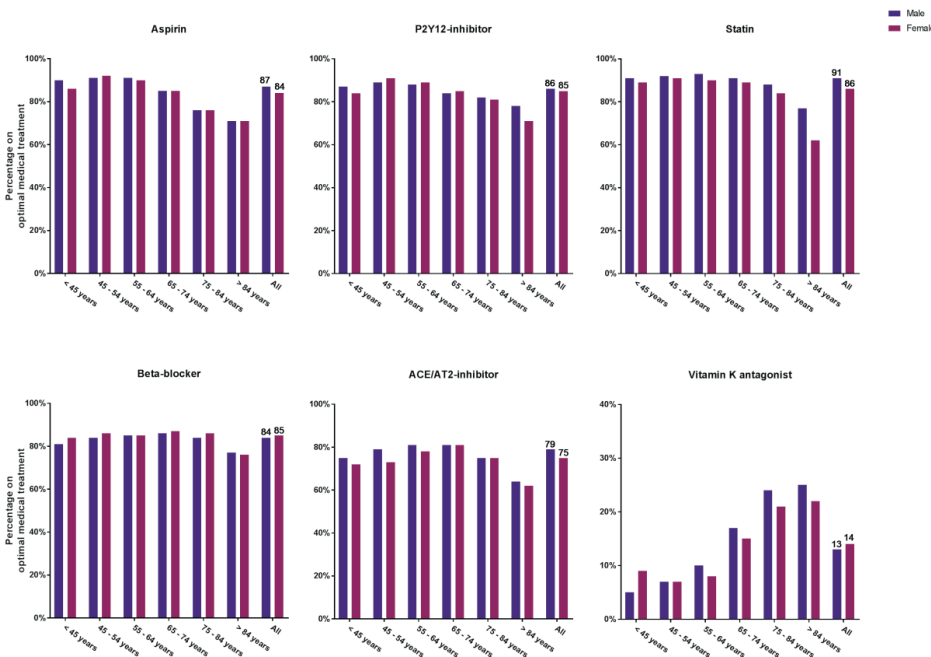


Figure 2: Medical adherence during one year after STEMI.

Specific subgroups

In patients younger than 45 years, medication after STEMI is similar to middle aged patients. However, following NSTEMI, patients are less often treated with beta-blockers

or ACE/AT2-inhibitors. Additionally, younger female patients receive treatment less often when compared to their peers or to middle aged patients. Furthermore, elderly female patients are least often treated with statins.

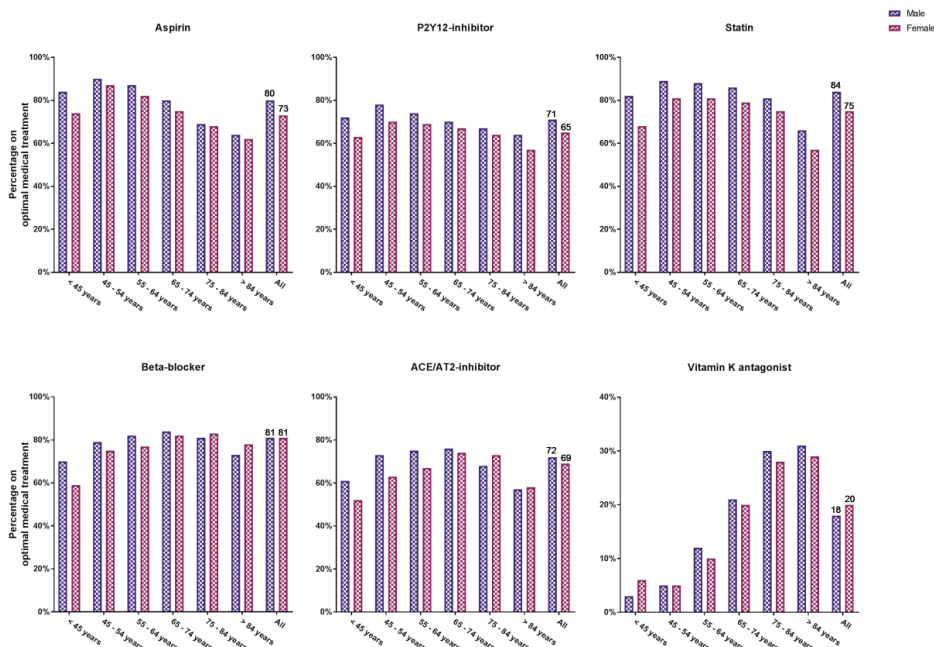


Figure 3: Medical adherence during one year after NSTEMI.

DISCUSSION

In the current study on medical adherence after acute myocardial infarction in the Netherlands, the findings can be summarized as follows: (i) 60% of STEMI patients and 40% of NSTEMI patients achieved optimal medical adherence; (ii) Medical adherence is lower in female patients and the elderly, especially following NSTEMI; (iii) important differences in medical adherence exist per age group, particularly in female patients.

STEMI versus NSTEMI patients

Despite pathophysiological differences between STEMI and NSTEMI, the ESC guidelines for medical adherence are nearly identical.^{4, 5} Double platelet inhibition is recommended for one year (or shorter in case of VKA or NOAC usage) and aspirin and statin usage is recommended life-long.^{4, 5}

Furthermore, beta-blocker and ACE/AT2-inhibitor use is indicated for patients with LV dysfunction (Class I, level A) and recommended if not contra-indicated in the remaining group (Class II, level A).⁴⁻⁶ When comparing this study with previous large registries, an additional improvement in medication adherence over time can be observed, suggesting an increased focus on adequate medication prescription after AMI.^{8, 13, 14} Additionally, the current study shows a higher medical adherence in STEMI patients, also observed in a study by Somma et al. in a voluntary registry at discharge in 72,352 patients.¹⁵ A potential cause for these differences can be that STEMI patients more often receive treatment by percutaneous coronary intervention and are more often treated in tertiary care facilities with more focus on guideline-based medicine than smaller centers without possibilities for intervention.¹⁵ However, the lower medical adherence in NSTEMI-patients could also be explained by a high percentage of female patients in which a conservative treatment is considered. This may relate to the risk-treatment paradox, which describes a treatment selection bias in which low-risk individuals are more likely to receive therapy than those patients at higher risk for poor outcomes.¹⁶ We elaborate more on the gender effect in the next section. Furthermore, whether receiving a PCI may affect the medical adherence, should be further studied.

Additionally, the use of medication has not been studied in patients with a type 2 acute coronary syndrome (secondary to non-cardiac causes, such as anemia, fever or tachycardia), who could be registered as a NSTEMI as well.^{4, 5, 17} When comparing the current results with previous studies such as the EUROASPIRE IV Study (2015), and the study of Koopman et al. (2013), an additional improvement in medication adherence over time can be observed, suggesting an increased focus on adequate medication prescription after an acute myocardial infarction.^{8, 14} To our knowledge, no previous studies were conducted, comparing medical adherence during longer follow-up in STEMI and NSTEMI on a national scale.

Gender differences

It is remarkable that the current study demonstrates that women are receiving less optimal medical therapy in all age groups and all drug categories (with exception of NOAC or VKA this was however prescribed in a small number of patients). Although this was observed in both STEMI and NSTEMI patients. It is particularly worse in the NSTEMI group. The clinical relevance of gender differences varies by age, type of infarction and type of medication. For example, small differences are observed in the use of beta-blockers, larger differences are observed in the use of statins. Previous studies have shown that the symptom pattern is more atypical in women, making it more difficult to diagnose cardiac pathology.^{18, 19} Additionally, women are still considered at lower risk of acute myocardial infarction, which makes physicians less aware of the risk of new cardiovascular events, causing lower

medical adherence. Smolina et al. confirmed these gender differences and showed that treatment was less often initiated in women.²⁰ However, once acute myocardial infarction has occurred, young women are at high risk of complications.²⁶ Although trials enrolled few women, benefits concerning safety and outcome have been observed regardless of gender.¹⁹ Data from this study stress the need for appropriate secondary prevention after acute myocardial infarction, especially in women and may be considered a wakeup call.

Age differences

Medication adherence in NSTEMI patients seems lowest in young patients and the elderly, especially in female patients. These important differences in medical adherence per age group, particularly in female patients, have been confirmed before.^{13, 14, 20-25} In the youngest patients (aged < 45 years) due to more atypical symptoms, a greater difficulty in certainty of diagnosis does exist.^{4, 18} Besides, elderly patients are least often treated, especially with statins. This could be due to the fact that older patients have increased prevalence of comorbid conditions and a higher risk for developing side-effects like bleeding, bradycardia and hypotension,²⁶⁻²⁸ which could result in a less favourable risk/benefit ratio with increasing age.²⁹ Additionally, discontinuation of medication or well-considered conservative treatment in elderly patients could be treatment of choice by physician or patient.^{30, 31} Finally, the physician's perception of lack of benefit from medical treatment could play a role. Treatment-benefits in elderly are scarcely tested in clinical trials. On the other hand, the potential beneficial effect of medical treatment is highest in the population with the highest risk of cardiovascular events: the elderly.^{23, 25} A cohort study in the of United Kingdom's Myocardial Ischaemia National Audit Project (MINAP) showed that potential survival gain by higher medical adherence after myocardial infarction is greatest in young patients but can be observed at all ages.²⁵

Strengths and limitations

This study evaluates nationwide pharmacy-epidemiological data in all myocardial infarction patients in the Netherlands in 2012 and 2013. Although these claims data provide less detailed individual patient information, there are no missing data and no loss to follow-up of patients, since all health care costs are registered, regardless of the hospital where care has been provided. Furthermore a previous validation of claims data study showed good reliability.³² However, some limitations have to be addressed. First, the data show retrieval from the pharmacy but do not differentiate if these drugs have actually been used by the patient. It is however reasonable to assume that patients who still after one year of follow-up do ask for drug delivery actually take the prescribed medication. Furthermore, detailed information about why patients are non-adherent is not evaluated. For example, contra-indications or intolerance to certain drugs could be an appropriate reason for discontinuation.

CONCLUSION

Age and gender differences exist in medical adherence after myocardial infarction. Medical adherence is lower in women, young patients and elderly patients, specifically in NSTEMI patients.

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Chapter 7

Mortality differences in acute myocardial infarction patients in the Netherlands: the Weekend-effect.

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ABSTRACT:

OBJECTIVE: Several studies have shown that patients admitted with an acute myocardial infarction during the weekends have a higher mortality rate than those admitted during weekdays, possibly attributable to less trained personnel available and a lower use of medical procedures. The current study aimed to assess this 'weekend-effect' in a nationwide registry.

METHODS: In the Netherlands, all inhabitants are, by law, obliged to have health insurance and all claim data are centrally registered. In 2012 and 2013, all national diagnose-codings of STEMI and NSTEMI patients were acquired. One-year mortality rates and treatment with percutaneous coronary intervention (PCI) were compared between weekdays and weekends (holidays included).

RESULTS: In total, 59,534 patients (67 ± 13 years, 39,545(66%) male) were included of whom 33,904(57%) had a NSTEMI. Overall 6,857(12%) patients died in the year following the acute myocardial infarction registration. In STEMI patients, no differences in one-year mortality rates were observed between admission on weekdays or weekends. In NSTEMI patients, one-year mortality was higher in those admitted during weekends (weekdays 11% versus weekends 13%, $p < 0.001$). Furthermore, STEMI patients admitted during weekends were more often treated with PCI (weekdays 77% versus weekends 81%, $p < 0.001$). Conversely, NSTEMI patients admitted during weekends were less often treated with PCI (weekdays 35% versus weekends 32%, $p < 0.001$).

CONCLUSION: Differences in treatment and mortality rates exist between acute myocardial infarction patients admitted during weekdays and weekends. NSTEMI patients admitted during weekends are less often treated with PCI and have a higher mortality rate than patients admitted during weekdays.

INTRODUCTION

Cardiovascular disease is the most frequent cause of death worldwide and in 2012, 7.4 million of those cases were attributable to ischemic heart diseases.¹ In case of an acute myocardial infarction, timely diagnosis and treatment, potentially with coronary intervention, is of utmost importance to achieve rapid revascularization and has a large impact on survival.^{2,3} Ideally, rapid access to emergency care should be equal at all time. As recommended by the ESC-guidelines for ST-segment Elevation Myocardial Infarction (STEMI), primary PCI should be performed by an experienced team within 90 minutes of the first medical contact.¹ However studies suggest that quality of emergency care may differ depending on the day of the week care is delivered. Several studies showed that patients admitted with an acute myocardial infarction on weekends had a higher mortality rate than those admitted on weekdays attributable to lower use of medical procedures.⁵⁻¹⁰ Conversely, other studies found no differences in mortality and conclude that a 'Weekend-effect' does not exist.¹¹⁻¹⁸

As in other Western countries, in the Netherlands, less personal is available in-hospital during weekends and an intervention team is on call and will be summoned in case of an indication for urgent intervention. Currently, a 24 hours in-hospital staff service is being debated, aiming to decrease treatment delays and improve prognosis.

The present study aims to assess whether there are differences in treatment and survival between patients with acute myocardial infarction (both STEMI and non-ST-segment Elevation Myocardial Infarction (NSTEMI)) admitted during weekdays or weekends in a nationwide population. In the Netherlands, all inhabitants are obliged by law to have health care insurance. Claim data of all hospitals, collected by the national insurance companies, serve as a unique opportunity to assess differences on a national level. Patients with STEMI or a non-ST-segment Elevation Myocardial Infarction (NSTEMI) are assessed separately.

METHODS

Setting

This study is a retrospective cohort analysis of prospectively collected claim data of the national insurance companies. In the Netherlands, inhabitants have an obligatory health insurance and immediate access to the health care system at all times. All diagnoses and treatments provided in the hospital are coded according to a national financial coding system. Insurance companies collect all hospital claims, which are registered centrally by the national center for Health Care data and information of the national insurance com-

panies (Vektis B.V., Zeist, The Netherlands). This database was used to assess differences in practice and outcome between weekdays and weekends.

Study population

All patients admitted in 2012 and 2013 with a STEMI (coded as 0320.11.204) or a NSTEMI (coded as 0320.11.205) were included. In case of multiple diagnose codes within the study period, the date of the first admission code was used for the analysis. For the analysis of all acute myocardial infarction patients, unique patients were analyzed and subsequently only the first STEMI or NSTEMI code was used. Patients were grouped by diagnose (STEMI or NSTEMI) and by admission day of the week. Since national holidays (22 in 2012 and 2013) also have a reduced in-hospital staff service, holidays are combined with Saturdays and Sundays in the Weekend analyses. Of all patients, age, gender and treatment (PCI or no PCI during admission), were registered at baseline.

Follow-up

Mortality was registered at 6 months and 12 months after inclusion. Mortality data were retrieved from the Vektis database in which de-registration from the insurance company with given reason 'dead' is recorded. Data from the national claim database was validated by comparing national claims data of four representative hospitals to local data, which is obtained by local patient records review. The overall accuracy was above 95%.¹⁹

Statistical analyses

Continuous data are presented as mean $\pm$ standard deviation. Categorical data are presented as number and percentages and compared by performing a Fisher's exact test. National data were analyzed using SAS® Version 9.3 (SAS Institute, Cary NC). Data on treatment (PCI vs no PCI) and outcome will be compared between weekdays and weekends, STEMI and NSTEMI were analyzed separately.

Ethical considerations

For the use of anonymized national data, permission of the national insurance companies was provided.

Funding statement and contribution statement

This work was supported by a grant of the Stichting Kwaliteitsgelden Medisch Specialisten (SKMS, Foundation Quality Funds Medical Doctors). The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

RESULTS

Patient characteristics

In 2012 and 2013, 59,534 patients were admitted for treatment of an acute myocardial infarction, mean age was 67 ± 13 years, 39,545 (66%) were male and 25,630 (43%) were diagnosed with STEMI. (Table 1) Treatment with PCI was performed in 31,638 (53%) of all patients. Overall, 6,862 (12%) patients died in the year following the acute myocardial infarction.

Table 1: Baseline characteristics

	Total
Total number of patients	N = 59,534
Age (yrs)	67 ± 13
Male gender	39,545 (66%)
Final diagnosis	
STEMI	25,630 (43%)
NSTEMI	33,904 (57%)
Treated with percutaneous coronary intervention	31,638 (53%)

Of all patients, 44,503 (75%) were admitted during weekdays and 15,031 (25%) during the weekend. Of these weekend-patients, 1,617 (11%) were admitted on a national holiday. In general, a sub-analysis of holidays compared to weekend-days showed no differences in mortality or treatment. Patients were more often admitted on a weekday (88 patients/day versus weekends 67 patients/day). (Figure 1) During weekdays, most patients were admitted on Monday (99 patients/Monday). During the weekends, especially a drop in the number of NSTEMI-patients admitted was observed (weekdays 51 patients/day versus weekends 35 patients/day).

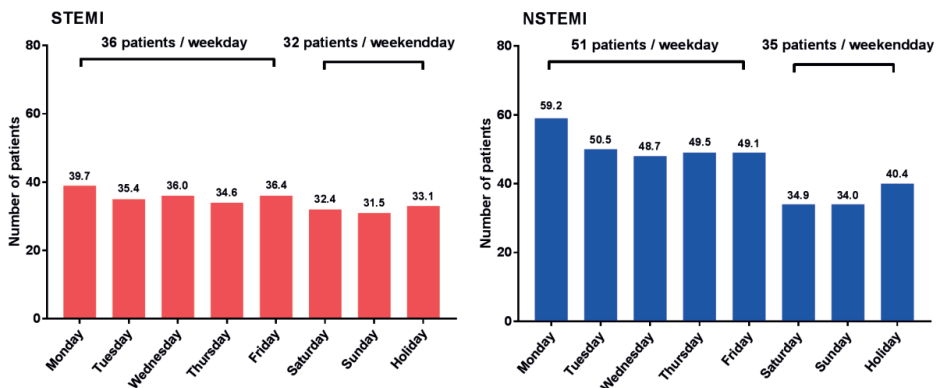


Figure 1: STEMI and NSTEMI registration per day of the week.

STEMI

Out of 25,630 STEMI-patients (mean age 65 ± 13 years, 69% male gender) the majority (72%) was admitted during weekdays.(Table 2) Additionally, the number of STEMI-admissions was higher on weekdays (36 patients/weekday versus 32 patients/weekend-day), with the highest number of admissions on Monday (39.7 patients/Monday).(Figure 1) Baseline characteristics (age and gender) between weekdays and weekends were similar.

Table 2: Patient characteristics in STEMI patients.

	Total	Weekdays	Weekends	Saturdays & Sundays	Holidays
Total number of patients	N = 25,630	N = 18,450	N = 7,180	N = 6,452	N = 728
Age (yrs)	64 ± 13	65 ± 13	64 ± 13	64 ± 13	64 ± 13
Male gender	17,879 (70%)	12,805 (69%)	5,074 (71%)	4,561 (71%)	513 (70%)
Deceased <180 days	2,627 (10%)	1,897 (10%)	730 (10%)	661 (10%)	69 (9%)
Deceased <365 days	2,986 (12%)	2,169 (12%)	817 (11%)	740 (11%)	77 (11%)
Treated with PCI	20,016 (78%)	14,165 (77%)	5,851 (81%)	5,257 (81%)	594 (82%)

Weekends are Saturdays and Sundays combined with national holidays.

Treatment with PCI was performed in 20,016 (78%) of all STEMI-patients. However, during the weekends, more STEMI-patients were treated with PCI (weekdays 77% versus weekends 81%, $p < 0.001$). (Figure 2) One year after STEMI registration, 2,986(12%) patients died of whom 2,627(10%) during the first six months. No differences in mortality rates were observed between weekdays and weekends.

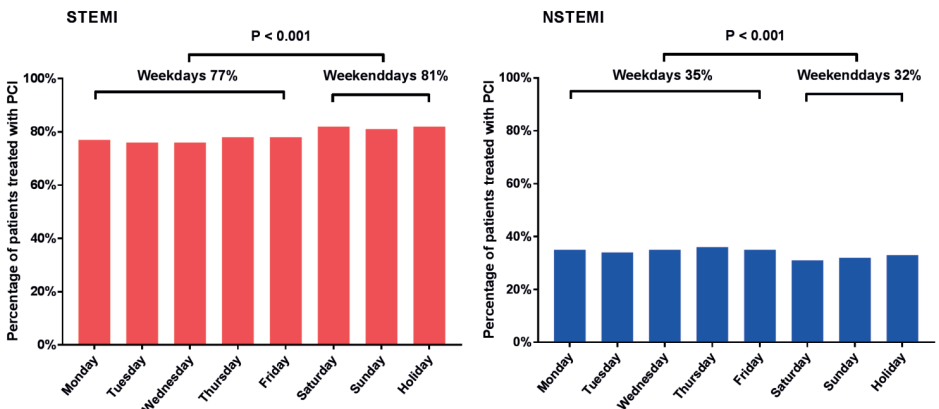


Figure 2: STEMI and NSTEMI patients per admission day of the week for receiving a PCI treatment during their admission.

NSTEMI

In general, NSTEMI patients ($n=33,904$) were older (mean age 69 ± 13 years) and the proportion of male gender was smaller (64%) compared to STEMI patients. (Table 3) Registration of NSTEMI was higher during weekdays (51 NSTEMI patients/weekday versus 35 STEMI patients/weekend-day), with the highest number of admissions on Monday (59 patients/Monday). (Figure 1) Baseline characteristics (age and gender) between patients admitted during weekdays and weekends were comparable.

Table 3: Patient characteristics in NSTEMI patients.

	Total	Weekdays	Weekends	Saturdays & Sundays	Holidays
Total number of patients	N = 33,904	N = 26,053	N = 7,851	N = 6,962	N = 889
Age (yrs)	69 ± 13	69 ± 13	69 ± 13	69 ± 13	69 ± 13
Male gender	21,666 (64%)	16,701 (64%)	4,965 (63%)	4,406 (63%)	559 (63%)
Deceased <180 days	2,849 (8%)	2,119 (8%)	730 (9%)	664 (10%)	66 (7%)
Deceased <365 days	3,876 (11%)	2,881 (11%)	995 (13%)	897 (13%)	98 (11%)
Treated with PCI	11,622 (34%)	9,134 (35%)	2,488 (32%)	2,196 (32%)	292 (33%)

Weekends are Saturdays and Sundays combined with national holidays.

Treatment with PCI was performed in 11,622 (34%) of all NSTEMI-patients. Patients admitted on a weekend-day were less frequently treated with PCI during their admission than those admitted on a weekday (32% versus 35%; $p < 0.001$). (Figure 2)

Within one year after NSTEMI, 3,876 (11%) patients died, of whom 2,849 (8%) died during the first six months. Significant differences in mortality rates were observed between patients admitted during weekdays and weekends six months after admission (weekdays

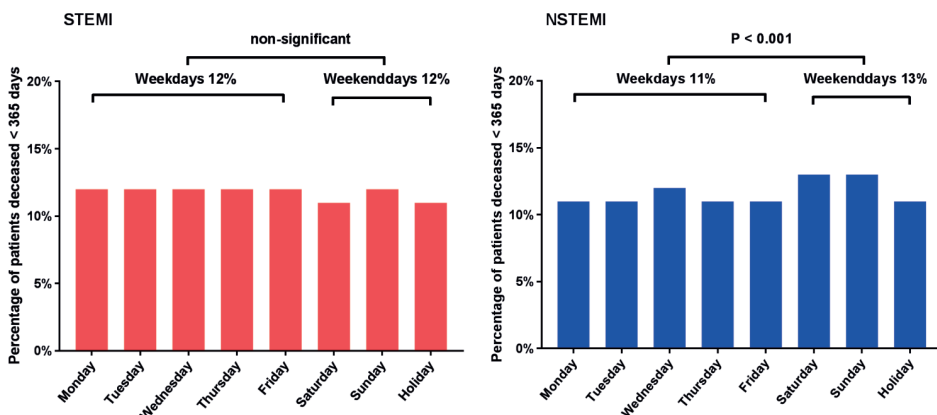


Figure 3: STEMI and NSTEMI patients per admission day of the week for mortality rate 365 days after admission.

8% versus weekends 9%, $p=0.001$) and one year after admission in NSTEMI patients (weekdays 11% versus weekends 13%, $p<0.001$).

DISCUSSION

In this study on the 'Weekend-effect' in patients with an acute myocardial infarction in the Netherlands, the findings can be summarized as follows: (i) NSTEMI-patients who are admitted during weekends are less frequently treated with PCI and have a higher mortality rate compared to NSTEMI-patients during weekdays; (ii) STEMI patients admitted during weekends are more often treated with PCI compared to STEMI-patients during weekdays; (iii) The admission rate for a myocardial infarction is higher on Monday and NSTEMI-patients are less often admitted during weekends compared to weekdays.

Treatment and mortality differences

Since the study of Bell et al. in 2001, various studies have been conducted to test the existence of a 'Weekend-effect', which postulates that reduced staffing leads to a higher mortality due to a longer time to intervention and lower rate of PCI during weekends.⁽²⁰⁾ Numerous studies show in acute myocardial infarction patients that this 'Weekend-effect' does not exist and that there is no significant difference in mortality between patients admitted to the hospital on weekends compared to weekdays.¹¹⁻¹⁸ However, other studies did find a significantly higher mortality and lower rates of performed interventions during weekends.⁶⁻¹⁰ Furthermore, a large meta-analysis of 48 studies by Sorita et al. showed a higher mortality during off-hours for both in-hospital and 30 day mortality, especially in STEMI patients.²¹ This may partially be attributed to longer door-to-balloon times during off-hours for STEMI-patients.

The current study shows a higher mortality rate in NSTEMI patients admitted during weekends (week 11% versus weekend 13%), which is possibly attributable to a lower number of PCI's performed during weekends (week 35% versus weekend 32%). However, a correlation analysis is not provided, only previous studies could support this hypothesis. A recent study of the British Myocardial Ischaemia National Audit Project (MINAP)-registry showed that the observed increased survival after NSTEMI was related to the higher use of invasive coronary strategies (such as PCI), more strongly than baseline clinical risk factors or an increased use of pharmacological therapies.²² No previous Dutch study concerning the 'Weekend effect' in NSTEMI patients is available.

In STEMI-patients, no mortality differences were found. This is in line with a previous single center study from the Netherlands, analyzing 4,532 STEMI patients with a primary PCI for

the incidence of all-cause mortality at 30-day and 4-year follow-up.¹⁷ In the Netherlands, a dedicated regional care collaboration between general practitioners, ambulance services and hospitals is assigned to provide consistent quality of care in patients with angina in order to close the mortality gap between off-hours and regular hours. After a pre-hospital electrocardiographic diagnosis is made by the ambulance, patients are immediately sent to the catheterization room which results in reduced ischemic times and a lower mortality, especially in STEMI patients.²³⁻²⁵ Moreover, acute coronary care for STEMI patients is organized in a limited number of specialized PCI-centers in the Netherlands. Probably, this strict pathway and dedicated regional collaboration for STEMI is the reason for the similar mortality during weekdays or weekends. Whereas the less stricter pathway for NSTEMI patients, could lead to a higher mortality ratio in NSTEMI patients during the weekends compared to weekdays. In which a delay in the acute treatment phase due to the diagnostic analysis at the emergency department or a lower number of available beds and treatment capacity could play a role. In this study, it is unknown whether this lower amount of performed interventions is due to the availability of competent staff admitted during weekends. Furthermore, the higher mortality ratio for NSTEMI patients during the weekends compared to weekdays may also be explained by a sicker population with more comorbidities. Previous studies, especially performed in STEMI populations, showed more severe patients (measured by the presence of cardiogenic shock or Killip Class) being admitted during weekends²⁶⁻²⁸, whereas other studies found no differences.^{15, 17, 29-32} Finally, age and gender differences between weekdays and the weekend could play a role. Other studies showed that mainly younger and male patients are admitted during the weekends.^{5, 8, 9, 11, 16, 26, 28, 29, 32} However, this study did not found differences in age and gender between weekdays and weekends in STEMI and NSTEMI, which is observed in other studies.^{7, 17, 27, 30, 31} Surprisingly, the STEMI patients admitted during weekends are more often treated with PCI compared to STEMI-patients during weekdays. This may be caused by the limited availability of catheterization rooms during weekdays due to scheduled elective procedures. In summary, previous studies show conflicting results on mortality differences during weekends or weekdays. This study shows differences in treatment and mortality on a national level. However, it remains unclear if mortality differences can be attributed to differences in treatment, patient population or national organization of health care.

Differences in patients admissions

A lower number of NSTEMI patients during weekends and a higher number of NSTEMI patients and even STEMI patients on Monday, could possibly be caused by patient delay or referral delay during the weekends. For acute presentations like STEMI and NSTEMI, one would expect no differences during the week-days and weekend-days. However, previous research in acute stroke care and the emergency department, also show an (unexplained) higher admission rate on Mondays.^{14, 33} Furthermore, a study by Willich et al. in 1994

showed an increased occurrence of acute myocardial infarction on Monday in the working population, according to the authors possibly being caused by a change in activity pattern and stress factors due to starting a workday.³⁴ More research is necessary to identify what kind of patients are admitted on Mondays.

Strengths & limitations

This analysis composes a large number of patients from a nationwide registry. The use of claim data is validated in a previous study.¹⁹ However, some important limitations should be addressed. First and as addressed before, due to the limitations of this claim data set, no adjustment for patient characteristics and treatment characteristics (staff availability, door-to-balloon times) is performed. Therefore, a final conclusion regarding the 'weekend-effect' is not possible. Secondly, no analysis could be done in which night-time versus day-time was assessed. However, previous registrations did not show large differences between night-time versus day-time and weekday versus weekend day.²¹ Third, this study is study is comparable to countries who has the same organization of care during the weekends. However, this manuscript shares its limitations with all weekend-studies. Large differences in patient characteristics, treatment characteristics and organization of care can differ per region and therefore the existence of a weekend-effect can differ.

International perspective

The national or regional organization of healthcare could be a factor in the existence of a 'Weekend-effect' and therefore current studies are supportive to explore the variation in quality of care (inter)nationally. Future analysis in the Netherlands is required to explore why differences exist and whether these are caused by patient factors (sicker patients) or organization of care (i.e. staff availability and strict care pathways), particularly in NSTEMI patients.

CONCLUSION

In the Netherlands, differences in treatment and mortality exist between acute myocardial infarction patients admitted during weekdays and weekends. NSTEMI patients admitted during weekends are less often treated with PCI during their hospital admission and have a higher mortality rate than patients admitted during weekdays.

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Chapter 8

Privacy of patient data in quality-of-care registries in cardiology and cardiothoracic surgery

The impact of the new General Data Protection Regulation EU-law

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ABSTRACT

Aims

Quality-of-care registries have shown to improve quality of healthcare and should be facilitated and stimulated. The data of these registries are potentially also very valuable for medical data research. While fully acknowledging the importance of re-using already available data for research purposes, concerns about how the applicable privacy legislation is dealt with exist.

Legal framework

In Europe, the new EU law on privacy, the 'General Data Protection Regulation' (GDPR) will come into force on May 25th 2018. One of the main rules is that non-anonymous patient data may, in principle, not be used for research without the patient's informed consent. When patient data are solely and strictly used for quality control and improvement this rule does not apply. It is especially important that registries take into account applicable privacy legislation because the GDPR makes it possible for national supervisory authorities to impose high fines to institutions in case of violation.

Implications

In this study we provide examples of quality-of-care registries in the field of cardiology and cardiothoracic surgery in Europe. None of the described registries (NHR, SWEDHEART and MINAP) currently ask specific informed consent of patients before using their data for medical data research. In order to comply with the new European data protection rules the advice to healthcare institutions is therefore to explicitly inform patients about the possible use of their data for quality-of-care registries while also designing a proper informed consent procedure to facilitate and optimize the use of quality-of-care data for medical data research.

INTRODUCTION

Privacy and confidentiality are core principles of a safe patient-physician relationship. Over a lifetime, important information about medical history, medication use, diagnostic tests and therapies is registered in patients' medical records. Medical information is considered to be a special category of data, as for most patients the disclosure of the fact that a person suffers from progressive heart failure, a psychiatric disorder or cancer is a far more sensitive aspect of their personal life than for instance the make of car they drive.¹ While in the past, data used to be registered and stored in the form of paper records, nowadays data is digitally collected and stored in Electronic Patient Records (EPRs) and easy accessible. Healthcare institutions handle large amounts of digital patient data in such records.²

Consequently data from EPRs are collected in centralized national quality-of-care registries.³ These data are very useful for secondary purposes, such as the monitoring of outcome measurements of hospitals and medical data research. The digital revolution and subsequent improvements in ICT have made it possible to collect and analyse large amounts of medical data.^{4, 5} The current availability of collected volume (with linking possibilities), velocity (real-time data) and variety (claim and clinical data) of data, leads to data becoming 'big data'.⁶ 'Big data' by definition refers to electronic health datasets so large and complex that they are difficult to manage with traditional soft- and hardware, nor can they be easily managed with traditional or common data management tools.³ By comparing and analysing 'big data' sets, it is hypothesized that efficiency and quality of healthcare may be improved and potentially at lower costs.

Privacy and data protection are an important and ongoing concern. Recently, multiple healthcare organizations in the United States have been the target of hackers stealing personal patient data with more than 1 million patients affected.⁷ Furthermore, in 2016 Hospital Trusts within the National Health Service (NHS) in England and Scotland were hit by a large ransomware attack, which resulted in locking computers and demands for payment for them to be unlocked.⁸ A different and perhaps more serious problem is that many medical organizations do not appear to be fully aware of the relevant legislation and the implications of using patient data for secondary purposes as monitoring of quality and medical data research.⁹ This not only create risks for healthcare professionals and institutions - varying from reputational damage to financial loss due to the high relating fines¹⁰ - but it may also have a negative impact on the patient-physician relationship.

In this study, first a few examples of quality-of-care registries in the field of cardiology and cardiothoracic surgery will be given. Next, a general overview of the European and Dutch legal framework (relevant data protection and privacy legislation) applying to quality-of-

care registries is provided. Finally, the specific implications of these laws and regulations for quality-of-care registries, what level of privacy protection is required, the potential problems in this regard and possible solutions are discussed. With respect to the latter, this article focuses on the future of these registries and make some recommendations.

QUALITY OF CARE REGISTRIES IN CARDIOLOGY AND CARDIOTHORACIC SURGERY

A quality-of-care registry is usually an independent organization maintaining a database containing information about a patient population with a specific disease, type of care or complication or a combination of these, that is used to measure, improve and report the quality of the care provided. The registry also organizes the processes to select and define the parameters. Monitoring quality of care primarily involves collecting and analysing and publishing specific patient data and results of the care delivered. Describing these in comparable patients using pre-specified variables, relationships and comparisons gives insight into how to improve the quality of care.¹¹ Healthcare providers collect data by entering data into a portal, by automatically linking electronic patient records or by delivering files with data. In most countries, 'raw' medical data cannot be owned, however health care providers have responsibilities towards patient data concerning certain patient rights, such as the patient's right to medical confidentiality.

After the data collection phase, the data files are securely stored after being encrypted by the registry. Subsequently, these aggregated data are analysed and adjusted by the agency that is responsible for the registration, then prepared for publication. The results are reported back to the healthcare providers themselves but also to the public and to other specific stakeholders, such as healthcare insurance companies, regulatory agencies and patient's groups. When combining different databases, a third trusted party acts as an intermediary who links encrypted data with personal identifiable data (e.g. date of birth). To ensure the quality of the data analysis, registries comply to international standard frameworks for information security, such as NEN 7510 (for securing of data), 7512 (for exchanging data) and 7513 (for logging and access to data).¹²

Three national quality registries in cardiology and cardiothoracic surgery in the Netherlands, Sweden and United Kingdom will be described. For each registry will be discussed how they handle privacy and informed consent issues. An overview is provided in **Table 1**.

National Registries in Cardiology – The Netherlands

The Netherlands Heart Registration (Nederlandse Hart Registratie, NHR) is the major cardiovascular quality-of-care registry in the Netherlands.¹³ The registry was initiated by healthcare professionals involved and funded by participating departments.¹⁴ Outcome indicators for cardiothoracic surgery, acute coronary syndromes, percutaneous coronary intervention, transcatheter heart valve implantations, ablation of atrial fibrillations and device implantations are included. The aim of the NHR is to improve quality of care by reporting outcome indicators in yearly publicly accessible reports. The NHR has a NEN-7510 certification. Encryption is used to pseudomize personal data.^{15, 16} Participating hospitals are responsible for data collection and registration and remain the owners of these data.¹⁷

National Registries in Cardiology – Sweden

Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART) is a Swedish quality-of-care registry in Sweden that reports the outcome of hospitalised patients with respect to acute coronary syndrome and coronary or valvular intervention.¹⁸ Every hospital in Sweden takes part in the registry which is publicly funded. A personal identity number is used by healthcare authorities in medical records. All quality registries are regulated by the Swedish Patient Data Act (2008:355).¹⁹ According to this act, caregivers are allowed to use personal data entered in a registry for the primary purpose of developing and securing the quality of care. Before personal data are entered in a registry, the responsible authority has to inform the patient. The patient may oppose registration, but the law does not impose a requirement of any (signed) consent from the individual.²⁰

National Registries in Cardiology – Great Britain

In the United Kingdom, Myocardial Ischaemia National Audit Project (MINAP) is the quality-of-care registry for myocardial infarction that collects the outcomes of patients in England, Wales and Northern Ireland. MINAP was started in 2000 and all 230 acute care hospitals in these regions participate in the registry. More than 1.300.000 patient records have been included. MINAP never publishes information that could lead to identification of individual patients, because patient records are cleaned and anonymised. Informed consent is not asked. MINAP conforms to legislation within the relevant Data Protection Act for the collection and use of patient identifiable data. Section 251 of the NHS Act 2006 allows the common law duty of confidentiality to be set aside in specific circumstances where patient consent is not attainable.

In summary, although the specifics of the saved personal data and omission of identifiable data differ somewhat between these three described European registries, they all secure data by encoding and use so-called Privacy Enhancing Techniques. None of the registries

ask the patient for informed consent to use their data in the quality-of-care registry. All of these registries carry out medical data research using the collected patient data.

LEGAL FRAMEWORK

Requirements following from international and European regulations

Quality-of-care registries collect and process large amounts of patient data, not only to use them for monitoring simply the quality of care within a single institution, but also to improve quality of healthcare (amongst others by publishing data analyses) and to stimulate medical data research. To facilitate this type of research, long-term storage and data linkage are prerequisites.²¹ The latter is significant because the legal provisions applying to setting up and using patient data purely for quality monitoring and the provisions for carrying out medical data research (and setting up research databases) are not the same.

The main rules concerning patient data are provided by binding legislation from the European Union (EU). From 1995 until 2018, the governing EU legislation was the European Privacy Directive (Directive 95/46/EC) on processing of personal data.²² In 2012, the European Commission of the EU proposed a comprehensive reform of the EU's privacy directive. A strong and more coherent data protection framework in the EU seemed necessary in light of rapid technological developments and globalisation, which brought new challenges for the protection of personal data. The new EU law, the 'General Data Protection Regulation' (GDPR), was adopted in April 2016 and will come into force on May 25th 2018.¹ The GDPR does not require implementation and is directly applicable in all member states to ensure a consistent and high level of protection of individuals. The GDPR makes it possible for national supervisory authorities to impose high fines to institutions in case of violation.

The leading principle of the GDPR, as included in article 9, is that the processing of personal data is prohibited, but it is allowed in specific cases set out in the GDPR. Proving explicit informed consent is an example of such an exception as well as data processing for health care purposes.

When patient data are used for monitoring quality of care within healthcare institutions, article 9, paragraph 2 sub i of the GDPR is applicable. It allows collection and use of personal data to manage healthcare systems or to guarantee high standards of quality of care.²³

However, if quality-of-care data are used for medical data research, a stricter legal regime for the processing of the collected data should be taken into account. The main rules

are provided by the same binding legislation from the EU,²⁴ the GDPR. From article 9, paragraph 2 sub j GDPR follows that collection and use of personal data for medical data research is allowed when this is done in accordance with the principle of proportionality and the purpose of the research while appropriate measures have been taken to protect the rights of the individual subjects.²³ Appropriate measures include collecting the smallest amount of data necessary for research and the anonymisation of data when possible. An overview of the most important consequences of the GDPR for healthcare organisations and quality-of-care registries is provided in **Table 2**.

Because EU-law offers a general legal framework and does not specifically address medical data research, non-binding rules developed by the Council of Europe and the European Science Foundation could provide further guidance. The main principles are that non-anonymous or identifiable medical data may only be collected and analysed, if this is necessary for carrying out the research and if the data subjects have given their informed consent. However, where it would be unrealistic to seek the individual's consent, personal data may still be collected and used, provided that certain conditions are met. One of these conditions is that the patient knows about the possible use of his or her data for medical data research (right to be informed on a general level) and has not objected to this (right to opt out).²⁵

Requirements following from Dutch law

In the Netherlands, according to the Dutch law on Quality, Complaints and Disputes in Healthcare (*Wet kwaliteit, klachten en geschillen zorg*),²⁶ it is considered an obligation of each healthcare institution to collect and register quality-of-care patient data and to use these for monitoring, assessing and improving the quality of the care provided to patients. The latter law contains no specific requirements on the protection of patient data. As mentioned before, in the Dutch cardiovascular quality-of-care registry (NHR) participating hospitals are responsible for data collection and registration and remain the owners of these data.¹⁷

Compared to the number of scientific publications from the Swedish and British registry, the Dutch cardiovascular registry only published a few papers in scientific journals with data published in yearly reports before. When quality-of-care data are used for medical data research purposes, apart from the GDPR and its additional provisions on a national level, the Medical Treatment Contract Act (*Wet op Geneeskundige Behandelovereenkomst*, referred to as WGBO, a section of the Dutch Civil Code) is particularly relevant because this law contains specific rules on data processing for medical data research. The main requirement is patient consent (Article 7:457 Civil Code). However, when it is reasonably not possible (patient is deceased or untraceable) or feasible (large amount of patients, large chance of

non-respons) to obtain consent the requirement for consent may be put aside. Then, data may only be collected from patient records if they have been pseudonymized in advance. In the event of a 'consent-waiver', three additional conditions need to be met. First, the research project should serve a public interest. Second, the research could not be carried out without the data concerned. Third, the data subject is informed about the possible use of data for research projects and has not explicitly opposed to this.

In the Netherlands, the Data Protection Authority (*Autoriteit Persoonsgegevens*) is the national supervisory authority on the processing of personal data by healthcare institutions.²⁷ The Dutch DPA can, similar to other EU supervisory agencies, impose high fines if the law and its legal requirements are violated.

IMPLICATIONS FOR QUALITY-OF-CARE REGISTRIES

Quality-of-care registries collect and process large amounts of patient data. The registries in the field of cardiology and cardiothoracic surgery described before not only use patient data for monitoring simply the quality of care within a single institution, but also to improve quality of healthcare (amongst others by publishing data analyses) and to stimulate medical data research.

As pointed out before, the rules for using data for medical data research are stricter than for purely quality monitoring. In most jurisdictions, based on the GDPR, one of the most important difference between the two legal regimes is that patients have control over the use of their data for medical data research – in the form of an opt-in or opt-out possibility – while this position is absent in the context of data processing for quality of care monitoring. According to Dutch law, the basic requirement in this respect is that informed consent of patients should be obtained for using their data for research, although the law leaves room for exceptions if research would become impossible or infeasible.

Another 'escape' from the stricter rules for using medical data for research would be to collect and use truly anonymous data, because in that situation data protection and privacy legislation do not apply. Anonymised data is no longer considered personal data in the context of the GDPR and the national data protection legislation and handling those data is considered not to interfere with the privacy of the participating patients.²⁸ Registry data could only be considered truly anonymous if disproportionate effort is required to link the data to identifiable patients.

The best practices for complete anonymisation of data in clinical trials could be used for complete anonymisation of data in quality of care registries also. Data from datasets can be classified into either direct identifiers or indirect identifiers, where direct identifiers (like name and initials, address including postal code) have a high risk of identifying a patient and indirect identifiers (like rare treatment, place of birth) could lead to identification.²⁹

To anonymize a data set, it is advised in the literature to remove direct identifiers and to remove certain indirect identifiers (depending on the risk, p.e. indirect identifiers with small numbers are considered a high risk), recoding codes that identify patients with a new code and replacing date of birth (with age) and all patient related dates. Risky indirect identifiers could be modified if they are important for meaningful data analysis.³⁰ Whether indirect identifiers should be removed, modified or left, should be left to a relevant advisory body, either an ethics committee or appropriate national advisory body.²⁹

Although in many quality-of-care registries, data are pseudonymised by using privacy enhancing techniques, the data contained in the described cardiology and cardiothoracic surgery registries are not truly anonymous and therefore do not escape from the consequences of the privacy and data protection legislation. First, some - but not all - identifiable data are omitted. For example if a 87-year patient undergoes a specific, not so frequent procedure at this age (e.g. a coronary-artery-bypass-grafting including mitral valve replacement), data could still be retrieved to this individual patient, although date of birth has been omitted in the database. Secondly, the source of the data is not deleted at the time of data collection (hospitals have even an obligation to store patient data in the electronic patient records for a fixed period of time). Since it is difficult - but with reasonable effort not impossible - to trace data back to individual patients, the data in these registries should be considered as pseudonymised and not anonymised.

CONCLUSION

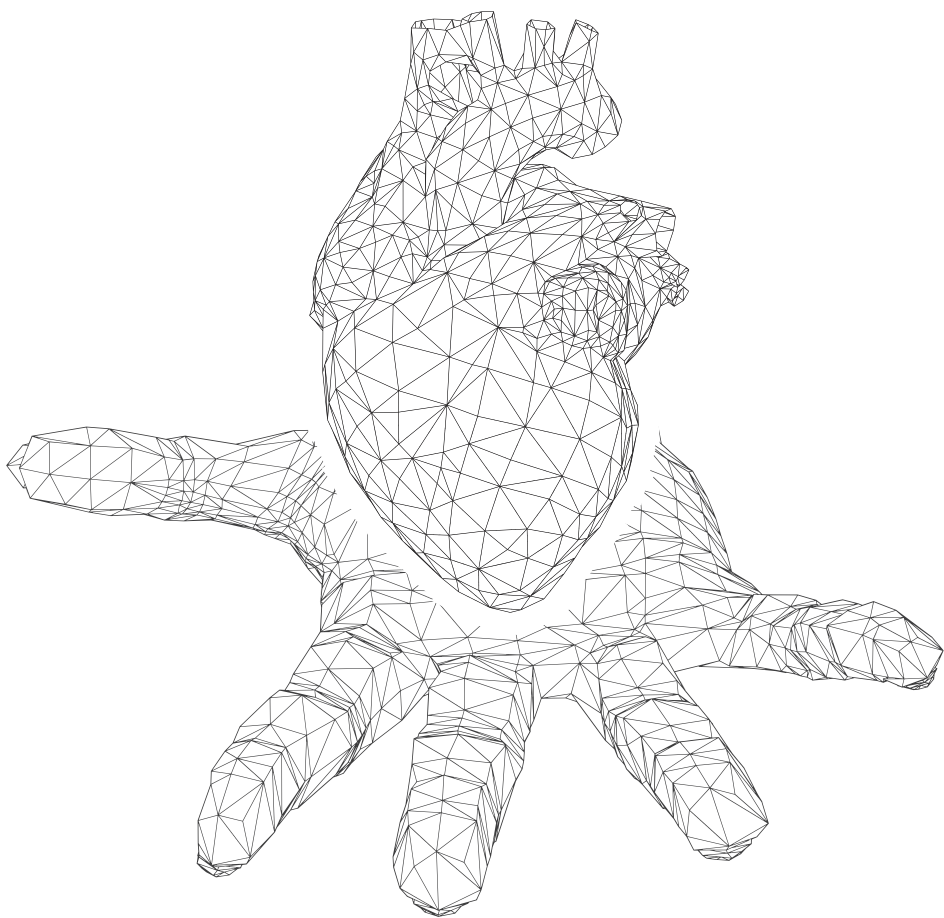
It is beyond discussion that quality-of-care registries improve quality of healthcare and should be facilitated and stimulated.¹⁴ In some countries, such as the Netherlands, this is even a legal obligation. Unless the personal data collected for and stored in these registries are completely anonymised, they fall within the scope of data protection law and regulations (the GDPR sets high standards for anonymisation and will be applicable in EU member states as of May 25th 2018). This implies that such data, in principle, may only be used for medical data research purposes after informing patients and obtaining their explicit consent. Some jurisdictions, such as the Dutch one, provide for exceptions (opt-out system) when research would be disproportionately hampered.

Proper information and consent procedures require considerable effort of healthcare institutions although IT-developments could make it increasingly more easy to implement. However, national supervisory authorities could impose high fines to institutions in case data protection and privacy regulations are not observed. Besides, by doing so, healthcare institutions invest in a trustworthy patient-physician relationship and they open new possibilities for researchers, such as the linking of international medical databases for future research. In order to comply with the new European data protection rules, embodied in the GDPR, the advice to healthcare institutions is therefore to explicitly inform patients about the possible use of their data for quality-of-care registries while also designing a proper informed consent procedure to facilitate and optimize the use of quality-of-care data for medical data research.

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**Summary, conclusion and
future perspectives**

**Samenvatting, conclusie en
toekomstperspectieven**

SUMMARY, CONCLUSION AND FUTURE PERSPECTIVES

The introduction (**chapter 1**, based on the published article 'The year of transparency: measuring quality of cardiac care') of this thesis describes the measurement of quality in the Dutch cardiac health care system. The definition of 'Quality', is described in four layers; 1. the ethical layer; 2. the professional standards and guidelines; 3. the legal layer and 4. quality indicators. This thesis focusses on the measurement of quality of care by quality indicators in patients treated for acute coronary syndrome and is separated in two parts: measuring patient safety on a local level (**Part I**) and measuring quality indicators on a national level (**Part II**).

The first part of the introduction describes the theoretical framework of patient safety. This thesis focusses on process deviations and the prevention of adverse events in patients treated for acute coronary syndrome and to define if our work process is sufficiently safe. In **chapter 2 to 4** this will be explained further.

The second part of the introduction describes the theoretical framework concerning measuring quality of care. The different types of indicators (structure-, process-, and outcome indicators) and stakeholders (patient, caregiver, health care insurance companies, supervisory boards and government) are discussed. Furthermore, the different mechanisms of actual improvement in health care by quality indicators are explained. Several (clinical) registries and quality indicators in daily cardiac care are described. The introduction concludes with defining the criteria of a good quality indicator (importance, reliable, valid, feasible, usable). **Chapter 5 to 8** of this thesis elaborates on the use of national claims data to measure quality of care in patients with acute myocardial infarction and evaluates patient's privacy the use of claims data.

Furthermore, the structure and content of the individual chapters will be discussed.

Part One - Quality of Care on a Local Level

Chapter 2 describes the development of a new valid instrument to objectively assess and monitor the occurrence of process deviations and adverse events in patients with acute myocardial infarction treated in a predefined care track. All 879 patients with a suspicion for an acute coronary syndrome and warranting coronary angiography in 2012 and 2013 were studied. All medical and nursery records were checked for process deviations (phase I) and whether any harm that occurred which was caused by (or due to inactivity of) the healthcare provider or the healthcare organisation (phase II). This was done by an adjusted version of the Harvard Medical Practice Study. A process deviation is defined as every operation or treatment that differed from the MISSION!-protocol, such as additional pro-

cedures, prescription of extra medication other than described in the protocol or omission of a procedure. An adverse event is defined as an unintended injury that results in disability at the time of discharge, death or prolonged hospital stay and is caused by healthcare management rather than by the patient's underlying disease process. Of all patients, 40% had a process deviation. One third ($n = 116$) of these had actually an adverse event during admission. The described method could be used as a template for developing a quality instrument of a patient record to objectify and monitor process deviations and potentially predicting and preventing adverse events.

Chapter 3 investigates the causal pathway of adverse events in patients with an acute coronary syndrome. The method is similar to the one used in chapter 2. Aim of this study was to assess the cause and the effect of adverse events in. In 13% of the 879 patients an adverse event occurred, of which 24% was preventable. Especially elderly, female patients and patients with an impaired renal function have a higher risk on experiencing an adverse event.

Chapter 4 describes why female patients more often experience adverse event in the treatment of an acute coronary syndrome and whether a 'risk-treatment-paradox' exists. The 'risk-treatment-paradox' is a situation in which patients at high risk for adverse events receive less intensive treatment compared to patients with a lower risk.¹ Again a patient record review of 879 patients is used. Of all 626 male patients, 10% had an adverse event, whereas in the group of 253 female patients, 21% had an adverse event ($P \leq 0.001$). Gender is an independent predictor of adverse events after adjustment for lifestyle factors, medication, comorbidities and treatment characteristics (odds ratio 2.4, $P \leq 0.001$). Furthermore, the 'risk-treatment-paradox' seems to exist. Women are less often treated according to international guidelines compared to man (less percutaneous coronary intervention (PCI) and longer symptom-to-needle-times), in which the increased risk for female patients is possibly underestimated.

Part Two - Quality of Care on a National Level

Chapter 5 evaluates whether claims data of the Dutch Insurance Companies, managed by Vektis B.V. is useful for quality measurement. National claims data are validated by comparison to local patient records in four representative hospitals in The Netherlands. The data were compared at three stages: 1) validation of diagnosis and treatment coding; 2) validation of the hospital where follow-up has taken place; and 3) validation of follow-up medical treatment, 365 days after the acute myocardial infarction (aspirin, P2Y12-inhibitor, statins, beta-blocker and angiotensin-converting-enzyme/angiotensin-2-inhibitor). The claims data were proven to be highly accurate. This offers an opportunity for the use of claims data in quality assessments of acute cardiac care.

Chapter 6 evaluates the secondary prevention care in The Netherlands, one year after acute myocardial infarction. Claims data of all acute myocardial infarction patients in The Netherlands from the national Hospital Information System of 2012 and 2013 are analysed and connected with the national Pharmacy Information System. In total, 59,534 (67 ± 13 year, 66% male) patients were included of whom 52,672 (88%) patients were analysed for one-year medical therapy adherence. STEMI (ST-segment elevation myocardial infarction) patients more often achieved optimal medical adherence than NSTEMI (non-ST-segment elevation myocardial infarction) patients (60% vs. 40%, $p \leq 0.001$). In both STEMI and NSTEMI, use of all five indicated drugs was higher in male patients compared to female patients (STEMI male 61% vs. female 57%, $P \leq 0.001$; NSTEMI male 43% vs. female 37%, $P \leq 0.001$). With increasing age, a gradual decrease was observed in the use of aspirin, P2Y12-inhibitors and statins.

In **Chapter 7**, claims data are used to analyse the 'weekend-effect' in the treatment of acute myocardial infarction. The 'weekend-effect' is a term used for a difference between patients admitted with an acute myocardial infarction on weekends when compared to weekdays, attributable to a lower quality of care (e.g. lower use of medical procedures). All STEMI and NSTEMI patients in the Hospital Information System in 2012 and 2013 were included (59 534 patients, 57% NSTEMI). In STEMI patients, no differences in one-year mortality rates were observed between admission on weekdays or weekends. However, STEMI patients admitted during weekends were more often treated with PCI (weekdays 77% versus weekends 81%, $P \leq 0.001$). In NSTEMI patients, one-year mortality was higher in those admitted during weekends (weekdays 11% versus weekends 13%, $p < 0.001$). Potentially this is related to a lower use of PCI's in NSTEMI patients admitted during weekends (weekdays 35% versus weekends 32%, $P \leq 0.001$). More research is necessary to explain the lower mortality rate for NSTEMI patients, admitted during weekend.

Chapter 8 concludes with the potential conflict of patient privacy and the collection of patient data in quality-of-care registries. While fully acknowledging the importance of re-using already available data for medical research purposes and improving quality-of-care, concerns about the way the registries deal with the applicable privacy legislation do exist. Based to the new (2018) European law, the General Data Protection Regulation, the advice is to explicitly inform patients about the possible re-use of their data stored in quality-of-care registries for medical research (and providing the opportunity to opt-out) and ask every patient their specific informed consent in the near future. In the patients' survey of 361 respondents, the majority agreed with sharing data with healthcare professionals or healthcare researchers. Similar results can be expected when permission is requested for a quality register within cardiology and cardiothoracic surgery.

CONCLUSION AND FUTURE PERSPECTIVES

Attention for vulnerable groups

The female heart

Although ESC guidelines for the treatment of an acute myocardial infarction are similar in male and female, there are differences in the treatment. Additionally, patients experience more adverse events.²⁻⁸ Other patient characteristics, such as age and frailty, only partly explain these differences (chapter 3 and 4). Furthermore, female patients receive optimal medical treatment less often after an acute myocardial infarction, specifically in NSTEMI patients (chapter 6). In the future, it is important to pay more attention to gender differences regarding disease presentation and under-treatment. The underlying reason for this may be the “risk-treatment paradox”: patients with a higher risk for adverse events receive less-intensive treatment (chapter 3 and 4). Since recently, the Dutch Society for Cardiology and the Dutch Heart Foundation pay more attention to the female heart by supporting scientific research and stimulating the participation of women in studies.⁹ The causes of adverse events in female patients should be studied, particularly in bleeding-related incidents. Although the ESC guidelines do mention the differences between male and female, currently no difference exists in the approach to diagnosis and treatment.^{7,8}

NSTEMI

NSTEMI patients are mentioned as an undertreated patient population. STEMI and NSTEMI share the same pathologic process to evolve to an acute myocardial infarction and have the same treatment to prevent arteriosclerosis and a recurrent acute coronary syndrome.^{10, 11} Due to the acute course, STEMI requires rapid therapeutic treatment. Because of this acute course, a higher mortality rate is expected in STEMI compared to NSTEMI patients. However, an increased mortality is observed in NSTEMI patients compared with STEMI patients, in particular on the long term.¹²⁻¹⁵ This is partly attributed to the higher age at admission and the occurrence of co-morbidities in NSTEMI patients.¹⁶⁻¹⁸ Differences in treatment and thus a ‘risk-treatment paradox’ could play a role as well. Despite the increased mortality risk, chapter 6 shows an under-treatment regarding the use of secondary drug prevention after admission for NSTEMI compared to STEMI. These results emphasize the importance of following the guidelines, especially in NSTEMI patients and female patients.

Elderly patients

Elderly receive secondary prevention less often (chapter 6) and have a greater risk of adverse events (chapter 3). It is expected that this will become even more important in the future, with the increase of the elderly population. In the hospital, attention is already being paid to this vulnerable group by means of the “Senior Friendly Hospital” quality

mark.¹⁹ This quality mark focuses on quality criteria such as the deployment of a geriatric team, attention for the elderly patient on the Emergence Care Department and care after discharge from hospital.

The assessment of quality of care

Local focus

Ideally, a setting could exist where high-risk moments in healthcare are identified on time, in order to adjust processes and prevent poor outcome. The importance of focusing on processes instead of focusing on outcome can be compared to a glass that falls due to a child playing too wildly. When focusing on the outcome, the child would only be corrected if a glass falls over during play (leading subsequently to an undesirable outcome). When focusing the process, one would correct the child's play, which automatically reduces the chance of an undesirable outcome. An increase in poor outcomes can be a trigger to investigate processes; it will be checked if children played too wild, when a striking number of glasses are broken. Therefore, analysing care data through structure, process and outcome indicators are of great importance and data-driven healthcare will become important in clinical practice on local and national level. Chapter 2 and 3 showed a method for process observation within the acute coronary syndrome care pathway. By observing the process deviations, an undesirable outcome can be predicted and ultimately prevented. In the future, real-time monitoring of risky processes can play a role in proactively controlling processes. In this, a patient with known risk factors for adverse event (e.g. female gender, higher age and poor kidney function) can be given a warning when planning a risky procedure. This requires specific attention for risk groups in education for physician assistants and cardiologists.

Furthermore, a cultural change on an entire department is important to regard quality and safety (First, do no harm!) as top-priority for all involved healthcare professionals. On a hospital department, attention is paid to incident analysis through incident reports, complaint procedures, Morbidity and Mortality Conferences and calamity reports. Using a traditional concept, called 'Safety-I', the goal of these meetings is to find solutions in order to prevent all future incidents and accidents ('Freedom from unacceptable risk'). However, complex work processes can go right or wrong. During these situations, the human adaptive power tries to compensate for the fact that clinical practice is always imperfect and variable.^{20, 21} 'Safety-II' assumes a resilient work environment ('Resilient healthcare') that adapts to changed systems and observes why it usually goes well. This fits with 'Just Culture' ideas of Sidney Dekker, in which everyone's role is taken into account without any judgement, but by clarifying everyone's responsibility. Anchoring a broader safety culture in a department is therefore a major challenge.

National focus

Furthermore, there is a national need for an inexpensive and efficient way of measuring quality of care. Various stakeholders in the healthcare sector (Inspectorate of Healthcare and Youth, health care insurers, National Healthcare Authority, audits (such as Q-mentum)) ask the hospitals and health care provider to justify the care provided and to deliver various indicators. A survey of the Federation Medical Specialists, Association of Arts and Auto and the general practitioners' initiative 'Het Roer Moet Om' in 2017, observed that physicians spend 40% of their time working on administration such as keeping medical records, checking diagnosis-treatment codes or acquiring data for quality and safety registries.²² Solely 36% of these actions are considered useful by physicians. The use of registered claims data to gain insight in care processes and quality of care plays an important role. This thesis proves that claims data from acute myocardial infarction patients and associated pharmacy claims data are very useful for efficient and valid quality measurement (chapter 5).

This national claims data can be used to gain insight into national financial flows. Furthermore, it can be used within quality-of-care measurements for more transmural insight. By linking various data registries, a patient can be monitored throughout the entire care process: from the first presentation with thoracic complaints at the general practitioner, followed by a treatment for acute myocardial infarction in the hospital, up to results about cardiac rehabilitation and long term follow-up. In addition, it offers the possibility of comparison of hospitals or regions. By analysing ambulance regions, postal code regions or hospital regions, regional variation can be mapped. As an example, the regional variation in preventive medication in the Netherlands by postal code is presented in Figure 1.²³ Regional analysis are useful for a targeted regional approach, in which care providers in one region (hospitals, general practitioners, Municipal Health Service (Gemeentelijke Gezondheidsdienst, GGD) and all paramedics in a region, pharmacists) are responsible for the health of patients living in that region. This is comparable to *Accountable Care Organizations*, in which healthcare providers and health insurers are jointly responsible for the health care costs and health of a population (for example a municipality or region). Furthermore, national (claims) data are already being used for Value Based Healthcare, with the aim to maximize value for the patient while minimizing healthcare costs.²⁴

The use of registered data such as claims data for quality of care assessments will increase in the future. A number of pitfalls must be mentioned here. With a large volume of data (big data), formulating a good research question in advance is important in order not to get lost in the amount of data. Additionally, it is important to collaborate with a data manager *and* a physician from the clinical field to develop a relevant quality analysis. At last, performing these analyses is expensive. Luckily, experience is gained on how claims

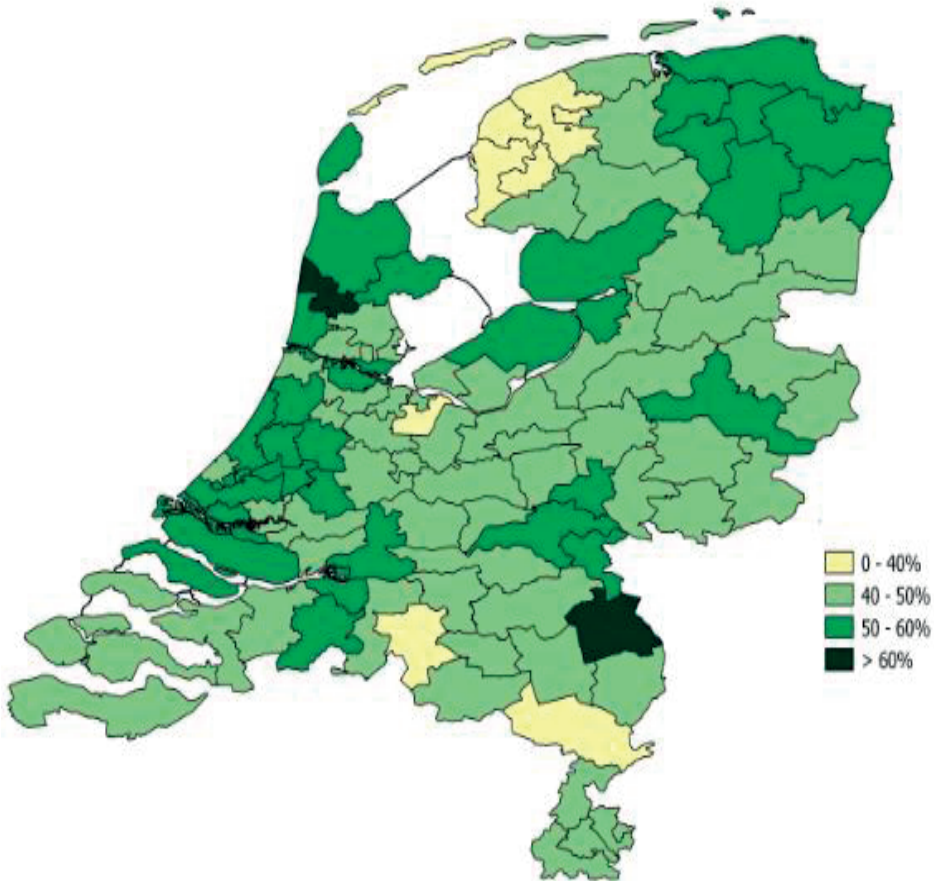


Figure 1: Optimal medical treatment in the Netherlands in 2012 and 2013.

Caption: Optimal medical treatment is defined as the use of acetylsalicylic acid, P2Y12 inhibitor, statin, beta-blocker and an ACE inhibitor one year after acute myocardial infarction.

data can be used for quality analyses (analysis per patient and process) in addition to financial analyses (analysis per procedure and volume), which may lead to a cost reduction in the future.

Publishing data

In the Dutch profession of Cardiology, a great reticence exist to publish quality data which can be traced back to individual centers or healthcare providers. In other professional groups in the Netherlands and in other countries, people are less negative about this. In Sweden, transparency on the quality of care based on outcome results contributed to an increase in quality and a decrease in costs.²⁵ Sweden, in particular SWEDEHEART (a cardiovascular clinical registry), has years of experience in publishing quality data (example in **figure 2**). The public health care organization ensures uniform criteria and specific

budget is available per county for the registration of clinical data.²⁶ The Swedish registries exist since 1987 and currently explores the possibilities of using registries for conducting scientific research by Registry-Randomized Controlled Trials.²⁷ Also in The Netherlands, several professional groups use national data for comparing the quality of care. The Dutch Society for Surgery has noticed positive results from the publication of national clinical data in the Netherlands.²⁸ Furthermore, linking clinical data and claims data in colorectal cancer surgery proofed that an increase in the number of complications in hospitals was associated with an increase in costs, and vice versa.²⁹

An important step in the comparison of quality of care within cardiology in the Netherlands is the Dutch Heart Registry, in which the various clinical registrations in cardiology (Meetbaar Beter, NCDR and BHN) are combined and use uniform criteria. This offers great opportunities to link national (claim) registries with detailed clinical information.³⁰ The national claims data of the insurers, as described in this thesis, can be used on a scientific level for the generation of outcome data and the transmural follow-up of the acute myocardial infarction patient. The clinical data from the Dutch Heart Registry can be linked with claims data, in order to gain more insight into underlying processes and possible options for improvement. The number of clinical variables per patient which are relevant to include in the registry could be discussed. A small dataset with basic elements, determined by the members of the Dutch Cardiac Society (Nederlandse Vereniging voor Cardiologie), can be registered annually and nationally.

Patient's privacy

For the patient, the quality records exhibit an improvement in the quality of care on a population level and an improvement in the insight into the quality of care of the various institutions and care providers. However, the privacy aspect of patient data also plays an important role in the use of care data. The owner of the data is initially the healthcare provider or institution, and after transfer of data to financial or clinical records, the owner is the person who manages and maintains these registrations. As long as the data are anonymous or data are linked by a Trusted Third Party, it will not interfere with the right to privacy of the patients. However, anonymous data can be traceable to a patient when a disease or treatment is rare. Therefore, Vektis B.V. maintains a limit of at least 10 patients per postcode area when sharing their data. The new legislation from Europe (General Data Protection Regulation (GDPR), as of May 25, 2018) is stricter regarding privacy. Especially when using quality records for scientific purposes, this requires good informed consent and an opt-out arrangement, next to reliable data security.³¹ This means that a patient must be informed about the fact that his data could be used for scientific research or quality-of-care analyses that serve the public health and that the patient has the possibility to remove his or her data from the databases at all times.

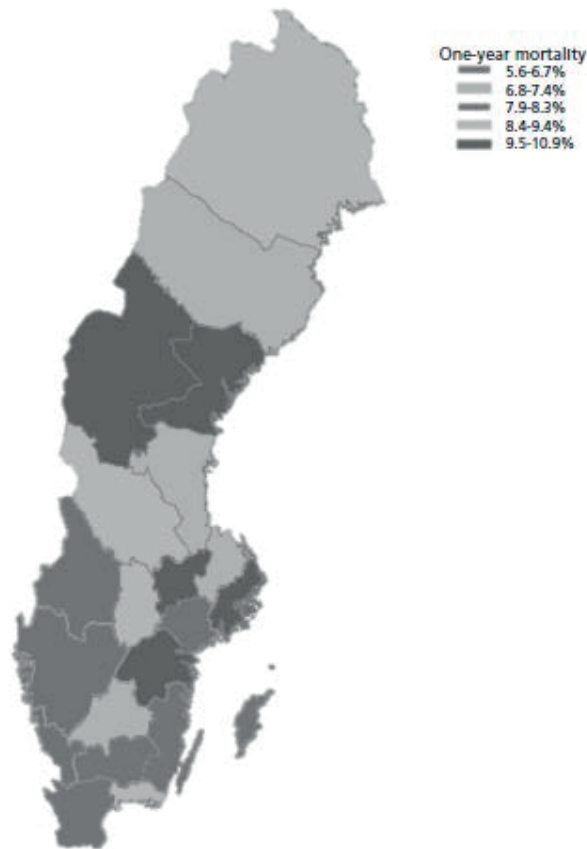


Figure 2: One-year mortality in acute myocardial infarction patients younger than 80 years in Sweden in 2015 – 2016, stratified per home county and per hospital.

Source: Jernberg T. Swedeheart - Annual report 2016. Uppsala, Sweden: Uppsala Clinical Research Center, 2017.³²

For publication and sharing results from quality-of-care research, the degree of traceability of the used data will always remain a discussion. Transparency of quality of care leads to improvement of care, in which the level of transparency depends on mutual trust of the involved care providers, authorities and patients.

Is our provided care 'sufficiently safe'?

This thesis focused on the question how one can measure the quality of care to assess whether the care provided for the treatment of acute coronary syndrome is sufficiently safe. Two methods were used: local record review study regarding patient safety (Part 1) and national claims data registration for quality-of-care research (Part 2). Claims data lack patient details, record review study research is laborious. The two different methods complement each other and serve a different purpose: safety and quality of care. The

provided care seems *safe*, yet 13% of the patients experience an adverse event. More research is necessary, but what kind of research? Record review study is very laborious and even research within a strict and clear working protocol as the MISSION!-protocol results in heterogeneous answers on the causal pathway of adverse events. Real-time monitoring of process deviations with registered data results in more insight in adverse events.

The provided care seems to have a *good quality of care* and to accord with the guidelines, yet only 49% of all the patients receive all five indicated medications after acute myocardial infarction. Herein there is room for improvement as well. Future analysis with claims data, combined with clinical data and other data sources, can provide more insight in order to continuously improve the quality of care.

NEDERLANDSE SAMENVATTING, CONCLUSIE EN TOEKOMSTPERSPECTIEVEN

De inleiding (**hoofdstuk 1**, gebaseerd op het gepubliceerde artikel '*The year of transparency: measuring quality of cardiac care*') van dit proefschrift beschrijft het kwaliteitsmeten in het Nederlandse zorgsysteem, in het bijzonder binnen de Cardiologie. Wat 'kwaliteit' is wordt beschreven in vier lagen: 1. de ethische laag; 2. de professionele standaarden en richtlijnen; 3. de juridische laag en 4. meten van kwaliteitsindicatoren. Het meten van de kwaliteit van zorg door middel van kwaliteitsindicatoren bij de behandeling van het acuut coronair syndroom is de focus van dit proefschrift. Het proefschrift is opgesplitst in twee delen: meten van patiëntveiligheid op een lokaal niveau (**Deel I**) en meten van kwaliteitsindicatoren op een nationaal niveau (**Deel II**).

In het eerste deel van de introductie wordt het theoretisch kader binnen het veiligheidsdenken beschreven. Dit proefschrift richt zich op procesafwijkingen en het voorkomen van zorggerelateerde schade bij patiënten die worden behandeld voor een acuut coronair syndroom en hoe wij kunnen definiëren of ons werkproces *veilig* is. Hier wordt verder op ingegaan in **hoofdstuk 2 tot en met 4**.

In het tweede deel van de introductie wordt het theoretisch kader omtrent het meten van kwaliteit van zorg beschreven. De verschillende indicatoren (structuur-, proces- en uitkomst-indicatoren) en rollen (patiënt, zorgverleners, zorgverzekeraars, toezichhouders en overheid) komen aan bod. Daarnaast wordt beschreven hoe kwaliteitsindicatoren via verschillende mechanismen een rol spelen in het daadwerkelijk verbeteren van de kwaliteit van zorg. De verschillende (klinische) registraties en kwaliteitsindicatoren in de dagelijkse cardiologische zorg worden beschreven. Tot slot beschrijft de introductie welke criteria belangrijk zijn voor een goede kwaliteitsindicator (important, reliable, valid, feasible, usable). **Hoofdstuk 5 tot en met 8** van dit proefschrift richt zich op het gebruik van nationale administratieve data voor het meten van kwaliteit van zorg bij patiënten met een acuut myocardinfarct en evalueert de patiënt privacy bij het gebruik van administratieve data.

Hieronder wordt nader ingegaan op de opzet en resultaten van de individuele hoofdstukken.

Deel Een - Kwaliteit van zorg op een lokaal niveau

Hoofdstuk 2 beschrijft het maken van een instrument waarin procesafwijkingen en zorggerelateerde schade worden geanalyseerd tijdens de behandeling in het ziekenhuis van patiënten met een verdenking op acuut coronair syndroom. Van patiënten in 2012 en 2013 (n=879) met een verdenking op een acuut coronair syndroom zijn het medisch en

verpleegkundig dossier bestudeerd met als doel om mogelijke procesafwijkingen (fase I) en schade door het (niet-) handelen van een zorgverlener of de zorgorganisatie (fase II) in kaart te brengen. Dit is gedaan aan de hand van een zelfontwikkelde methode welke is afgeleid van de Harvard Medical Practice Study. Een procesafwijking is gedefinieerd als elke handeling die afwijkt van het MISSION!-protocol door het uitvoeren van extra procedures, voorschrijven van extra medicatie anders dan het protocol of juist het niet-uitvoeren van een handeling. Zorggerelateerde schade (Engels: adverse event) is gedefinieerd als onbedoelde schade welke resulteert in tijdelijke of permanente schade op het moment van ontslag, verlengde ligduur of overlijden, welke is veroorzaakt door het handelen van zorgmanagement en niet door de onderliggend ziekte van de patiënt. Van alle patiënten blijkt zich bij 40% een procesafwijking te hebben voorgedaan. Bij éénderde ($n = 116$) van deze patiënten blijkt ook daadwerkelijk zorggerelateerde schade op te treden tijdens de opname. Deze methode kan een start zijn voor het ontwikkelen van een elektronisch tracking systeem binnen het elektronisch patiëntendossier. Een dergelijk systeem zou vervolgens ingezet kunnen worden voor continue monitoring van procesafwijkingen en om eventuele zorggerelateerde schade te voorspellen en te voorkomen.

In **hoofdstuk 3** wordt verder ingegaan op zorggerelateerde schade bij patiënten met een acuut coronair syndroom. De methode die hiervoor is gebruikt is identiek aan die van hoofdstuk 2. Het doel was om te kijken naar de oorzaken en het effect van zorggerelateerde schade. Van alle 879 patiënten ervaart 13% zorggerelateerde schade, waarvan 24% vermijdbaar is. Met name oudere patiënten, vrouwen en patiënten met een verminderde nierfunctie hebben een verhoogde risico op het ervaren van zorggerelateerde schade.

In **hoofdstuk 4** wordt bestudeerd of vrouwen vaker zorggerelateerde schade ervaren bij de behandeling van het acuut coronair syndroom dan mannen. De aanname dat vrouwen vaker zorggerelateerde schade ervaren is gebaseerd op de 'risk-treatment-paradox', een situatie waarin patiënten met een verhoogd risico voor schade minder intensieve behandeling krijgt dan patiënten met een lager risico.¹ Wederom is gebruik gemaakt van het dossieronderzoek bij 879 patiënten. Van alle 626 mannelijke patiënten, had 10% zorggerelateerde schade, waar in de groep van 253 vrouwen, 21% zorggerelateerde schade had. Het vrouwelijk geslacht blijft een onafhankelijke factor die van invloed is op het krijgen van zorggerelateerde schade nadat gecorrigeerd is voor leefstijl-factoren, medicatie, comorbiditeiten en behandelingskarakteristieken (odds ratio = 2.4, $R^2 = 0.036$, $P < 0.001$). Daarnaast wordt ook bewijs gevonden voor het bestaan van de 'risk-treatment-paradox'. Vrouwen worden minder vaak volgens de internationale richtlijnen behandeld (minder vaak PCI en langere symptoom-tot-naald-tijd), waarbij mogelijk het verhoogde risico bij vrouwen onderschat wordt.

Deel Twee - Kwaliteit van zorg op een nationaal niveau

In **hoofdstuk 5** is onderzocht of declaratiedata van de Nederlandse Zorgverzekeraars, welke beheerd worden door Vektis B.V. bruikbaar zijn voor metingen voor kwaliteitsdoeleinden. Nationale declaratiedata zijn vergeleken met lokale patiëntendossiers in vier representatieve ziekenhuizen in Nederland op 1) de diagnose en behandelingscodering; 2) waar de follow-up heeft plaatsgevonden; en 3) het gebruik van medicatie 365 dagen na het myocardinfarct (aspirine, P2Y12-remmer, statine, beta-blocker en angiotensine-converterend enzym/angiotensine-2-remmer) en dit bleek goed overeen te komen. Dit biedt mogelijkheden voor analyses naar kwaliteit van zorg binnen de acuut cardiologische zorg.

Hoofdstuk 6 geeft inzicht in de secundaire preventie zorg in Nederland, een jaar na myocardinfarct. De declaratiedata van alle myocardinfarctpatiënten in Nederland in 2012 en 2013 in het Ziekenhuis Informatie Systeem zijn geanalyseerd en gekoppeld met het landelijke Farmacie Informatie Systeem. In totaal zijn 59,534 (67 ± 13 jaar, 66% man) patiënten geïncubeerd waarvan 52,672 (88%) patiënten werden geanalyseerd voor medicatiegebruik na een jaar. STEMI (ST-segment elevatie myocardinfarct) patiënten gebruikten vaker alle vijf door de richtlijnen geïndiceerde medicatie na een myocardinfarct dan NSTEMI (non-ST-segment elevatie myocardinfarct) patiënten (60% vs 40%, $p \leq 0.001$). In beide infarct groepen hadden mannen vaker optimale behandeling (STEMI man 61% vs vrouw 57%, $p \leq 0.001$; NSTEMI man 43% vs vrouw 37%, $p \leq 0.001$). Met een toename van de leeftijd zie je ook een afname in het gebruik van aspirine, P2Y12-remmers en statines. Concluderend is medicatie gebruik na een myocardinfarct lager bij vrouwen, jonge patiënten en ouderen, in het bijzonder bij NSTEMI patiënten.

In **hoofdstuk 7** is declaratiedata gebruikt om het weekend-effect bij de behandeling van een myocardinfarct te evalueren. Hierbij wordt onderzocht of verschillen bestaan tussen de geleverde zorg in het weekend en door de week. Alle STEMI en NSTEMI patiënten in het Ziekenhuis Informatie Systeem in 2012 en 2013 zijn bekeken (59 534 patiënten, 57% NSTEMI). Bij STEMI-patiënten werd geen verschil gevonden in mortaliteit tussen een opname tijdens het weekend of doordeweeks. Daarbij werden STEMI patiënten in het weekend vaker behandeld met PCI (Week 77% versus Weekend 81%, $p \leq 0.001$). NSTEMI-patiënten die opgenomen werden in het weekend hadden een hogere één-jaars mortaliteit na het myocardinfarct (Week 11% versus Weekend 13%, $p \leq 0.001$). Mogelijk houdt dit verband met een lager aantal PCI's dat wordt verricht bij de patiënten die worden opgenomen in het weekend (Week 35% versus Weekend 32%, $p \leq 0.001$). Meer onderzoek is nodig om de lagere overleving bij NSTEMI-patiënten die in het weekend worden opgenomen te verklaren.

Hoofdstuk 8 besluit met het mogelijke conflict tussen de privacy van de patiënt en het verzamelen van patiëntgegevens in kwaliteitsregisters. Hoewel het belang van hergebruik van beschikbare gegevens voor medische onderzoeksdoeleinden en het verbeteren van de kwaliteit van zorg volledig wordt erkend, bestaat bezorgdheid over de manier waarop de kwaliteitsregisters omgaan met de privacywetgeving. Op basis van de nieuwe (2018) Europese wet, de General Data Protection Regulation, wordt geadviseerd om patiënten expliciet te informeren over het mogelijke hergebruik van hun gegevens die zijn opgeslagen in de kwaliteit van zorgregisters voor medisch onderzoek en de mogelijkheid te bieden om te kiezen voor opt-out. In een patiënten-enquête kwam onder 361 deelnemers naar voren dat de meerderheid toestemming zou geven voor het delen van gegevens met zorgprofessionals of onderzoekers in de gezondheidszorg.

CONCLUSIE EN TOEKOMSTPERSPECTIEVEN

Aandacht voor kwetsbare groepen

Het vrouwenhart

Ondanks dat de richtlijnen van de European Society of Cardiology (ESC) voor mannen en vrouwen voor de behandeling van myocardinfarct hetzelfde zijn, zijn er duidelijke verschillen in de behandeling van mannen en vrouwen en ervaren vrouwen vaker zorggerelateerde schade.²⁻⁸ Andere patiëntkenmerken als leeftijd en fragiliteit verklaren deze verschillen slechts deels. (hoofdstuk 3 en 4) Tevens wordt landelijk gezien dat vrouwen minder vaak met de juiste medicatie worden behandeld, in het bijzonder bij NSTEMI patiënten. (hoofdstuk 6) Voor de toekomst is het van belang dat meer aandacht wordt gegeven aan genderverschillen wat betreft de behandeling en symptomen. Onderliggend hieraan lijkt de 'risk-treatment paradox', waarbij het verhoogde risico bij vrouwen wordt onderschat bij de behandeling van het hartinfarct, alsmede het risico op zorggerelateerde schade. (hoofdstuk 3 en 4) De laatste tijd ontstond meer aandacht voor het vrouwenhart bij de Nederlandse Vereniging voor Cardiologie en de Nederlandse Hartstichting. Zij steunen wetenschappelijk onderzoek en daarnaast wordt de deelname van vrouwen binnen het wetenschappelijk onderzoek gestimuleerd.⁹ Specifiek is onderzoek nodig naar de oorzaken van zorggerelateerde schade, in het bijzonder bij bloeding-gerelateerde incidenten. Ondanks dat de ESC richtlijnen de verschillen tussen mannen en vrouwen wel benoemen, is er momenteel geen verschil in aanpak van de diagnostiek en behandeling.^{7, 8}

NSTEMI

Wederom komen NSTEMI patiënten naar voren als een onder behandelde groep patiënten. STEMI en NSTEMI delen hetzelfde onderliggende pathologische proces voordat

een hartinfarct zich ontwikkelt en hebben dezelfde behandeling voor het voorkomen van arteriosclerose en een recidief acuut myocardinfarct.^{10, 11} Echter het acute beeld bij een STEMI vraagt om sneller therapeutisch handelen. Vanwege het acute beeld bij STEMI wordt daar een hogere sterfte verwacht dan bij NSTEMI. Desondanks wordt, met name op langer termijn, een verhoogde mortaliteit gezien bij NSTEMI ten opzichte van STEMI patiënten.¹²⁻¹⁵ Dit wordt deels toegeschreven aan de hogere leeftijd bij opname en de meerdere comorbiditeiten bij NSTEMI patiënten.¹⁶⁻¹⁸ Verschillen in behandeling en daarmee een 'risk-treatment paradox' zouden ook een rol kunnen spelen. Ondanks de verhoogde kans op overlijden, toont hoofdstuk 6 een onder-behandeling wat betreft secundaire medicamenteuze preventie na de opname voor NSTEMI ten opzichte van STEMI. Deze resultaten benadrukken het belang van het adequaat volgen van de richtlijnen, met name bij patiënten met NSTEMI en vrouwen.

Ouderen

Door betere behandelingen worden patiënten ouder en zal de populatie oudere patiënten toenemen in de toekomst. De geconstateerde bevindingen, minder secundaire preventie bij ouderen (hoofdstuk 6) en grotere kans op zorggerelateerde schade (hoofdstuk 3), zullen dus in de toekomst toenemen. Binnen het ziekenhuis is reeds aandacht voor deze kwetsbare groep in de vorm van het keurmerk 'Seniorvriendelijk ziekenhuis'.¹⁹ Dit keurmerk richt zich op kwaliteitscriteria zoals de inzet van een geriatisch team, aandacht voor de oudere patiënt op de Eerste Hulp en nazorg na ontslag uit het ziekenhuis.

Het meten van kwaliteit van zorg

Lokale sturing

Idealiter wil je in de zorg een efficiënte manier ontwikkelen waarbij tijdig hoog-risico momenten worden geïdentificeerd zodat processen daarop aangepast kunnen worden en vervelende uitkomst voor de patiënt voorkomen kunnen worden. Het belang van sturen op processen in plaats van sturen op uitkomst kan worden vergeleken met een glas dat omvalt door een te wild spelend kind. Bij sturen op uitkomst, zou men het kind alleen corrigeren als er door het spelen een glas omvalt (en er dus een onwenselijke uitkomst ontstaat). Bij sturen op het proces, zou men het wild spelen van het kind corrigeren waardoor de kans op een onwenselijke uitkomst automatisch kleiner wordt. Een toename van negatieve uitkomsten kan wel een trigger zijn om processen te onderzoeken, als er ergens opvallend veel glazen vallen zal er gekeken worden of er te wild gespeeld wordt. Daarom zijn analyses van zorgdata middels structuur-, proces-, en uitkomst-indicatoren van groot belang en zal data-driven healthcare op lokaal en nationaal niveau meer en meer een rol gaan spelen in het werkveld. Hoofdstuk 2 en 3 toonde een methode voor procesobservatie binnen het myocardinfarct zorgtraject. Met het observeren van de benoemde procesafwijkingen

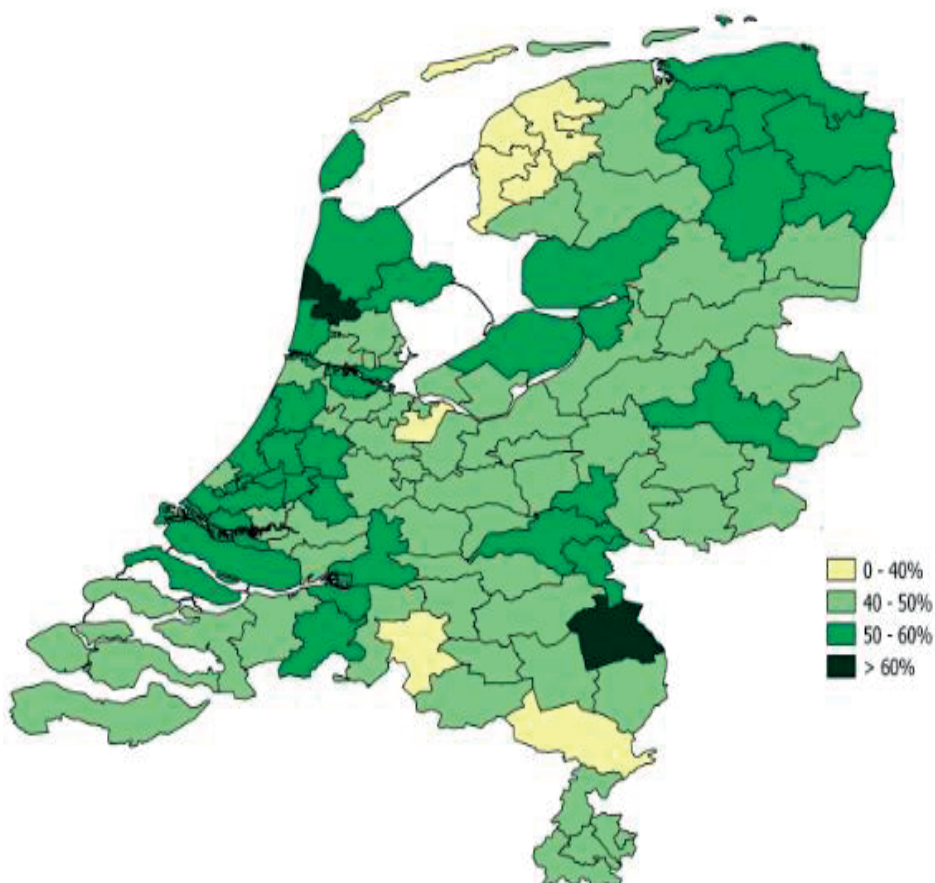
kan een onwenselijke uitkomst worden voorspeld en uiteindelijk worden voorkomen. In de toekomst kan real-time monitoring van risicovolle processen een rol spelen om proactief op processen te sturen. Hierbij kan bij een patiënt met bekende risicofactoren voor zorggerelateerde schade (bijvoorbeeld vrouwelijk geslacht en slechte nierfunctie) een waarschuwing worden gegeven bij het plannen van een risicovolle procedure. Dit vraagt om specifieke aandacht voor risicogroepen (*vrouwen, ouderen en patiënten met een verminderde nierfunctie*) in het onderwijs voor arts-assistenten en cardiologen.

Daarnaast is een cultuuromslag op een gehele afdeling van belang om kwaliteit en veiligheid (First, do no harm!) als prioriteit nummer 1 te hebben bij alle betrokken zorgprofessionals. Op een ziekenhuisafdeling is aandacht voor incidentanalyse middels incidentmeldingen, klachtenprocedures, complicatie- en calamiteitbesprekingen. Daarbij wordt volgens een traditioneel gedachtengoed, genaamd 'Safety-I', gezocht naar een oplossing tot afwezigheid van toekomstige incidenten en ongelukken bestaat ('Freedom from unacceptable risk'). Echter gaan complexe werkprocessen soms goed gaan of soms fout, waarbij het menselijke aanpassingsvermogen probeert te compenseren voor het feit dat de praktijk altijd imperfect en variabel is.^{20, 21} 'Safety-II' gaat uit van veerkrachtige werkvloer ('Resilient healthcare') die zich aanpast aan de veranderde systemen en kijkt naar wat maakt dat het meestal wel goed gaat. Daarin past 'Just Culture', waarin zonder oordeel wordt gekeken wordt naar ieders rol, zonder het benoemen van verantwoordelijkheden uit de weg te gaan. Het verankeren van een bredere veiligheidscultuur op een afdeling vormt een grote uitdaging.

Nationale sturing

Tevens is landelijk behoefte aan een goedkope en efficiënte manier om kwaliteit van zorg te meten. Verschillende partijen in de zorg (Inspectie Gezondheidszorg en Jeugd, zorgverzekeraars, Nationale Zorgautoriteit, audits (zoals Q-mentum)) vragen aan de ziekenhuizen en zorgverlener om het verantwoorden van de gegeven zorg en het aanleveren van verschillende indicatoren. Een inventarisatie van de Federatie Medisch Specialisten, Vereniging van Artsen en Auto en huisartseninitiatief 'Het Roer Moet Om' in 2017 toonde aan dat artsen 40% van hun tijd bezig zijn met administratie zoals het bijhouden van medische dossiers, diagnose-behandel-codes aanvinken of data invoeren voor kwaliteits- en veiligheidsregistraties.²² Slechts 36% van deze taken wordt door artsen zinvol geacht. Het gebruik van reeds geregistreerde declaratiedata om inzicht te krijgen in zorgprocessen en kwaliteit van zorg speelt een belangrijke rol. Uit dit proefschrift blijkt dat declaratiedata van myocardinfarct patiënten en bijbehorende medicatie data zeer goed bruikbaar zijn voor efficiënte en valide kwaliteitsmetingen (hoofdstuk 5).

Deze nationale declaratie data kunnen gebruikt worden om inzicht te krijgen in landelijke financiële stromen en ten tweede binnen kwaliteit-van-zorg metingen kan dit gebruikt worden voor meer *transmuraal inzicht*. Middels koppeling van verschillende databronnen is de patiënt in het gehele zorgproces te volgen: van de eerste presentatie met thoracale klachten bij de huisarts, waarna behandeling van het acuut myocardinfarct in het ziekenhuis volgt, tot aan hartrevalidatie en lange termijn follow-up. Daarnaast biedt het mogelijkheid tot een vergelijking van ziekenhuizen of regio's. Middels analyse van ambulance-regio's, postcode-regio's of ziekenhuis-regio's kan regionale variatie in kaart worden gebracht. Als voorbeeld wordt in **figuur 1** de regionale variatie van het medicatiegebruik in Nederland per postcode gepresenteerd.²³ Regio-analyses zijn bruikbaar voor een gerichte regionale aanpak, waarbij zorgverleners per regio (ziekenhuizen, huisartsen, Gemeentelijke Gezondheidsdienst (GGD) en alle paramedici in een regio, apothekers)



Figuur 1: Optimale medische behandeling in Nederland in 2012 en 2013

Bijschrift: Optimale medische behandeling is gedefinieerd als het gebruik van acetylsalicylzuur, P2Y12-remmer, statine, bètablokker en een ACE-remmer een jaar na het myocardinfarct.

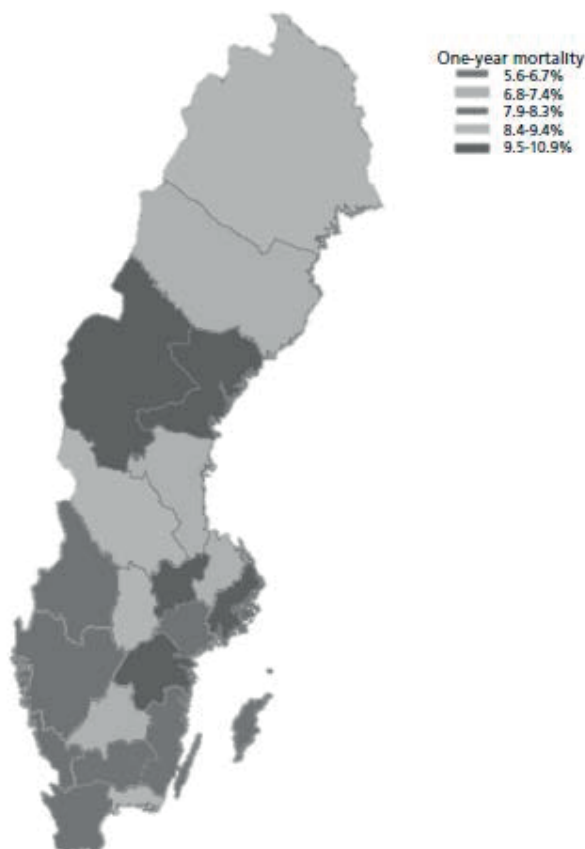
gezamenlijk verantwoordelijk worden gesteld voor de gezondheid van de patiënten die in die regio wonen. Dit lijkt op *Accountable Care Organisations*, waarbij zorgaanbieders en zorgverzekeraars gezamenlijk verantwoordelijk zijn voor de zorgkosten en de gezondheid van een populatie (bijvoorbeeld een gemeente of regio). Daarnaast worden landelijke (declaratie) data reeds gebruikt voor *Value Based Healthcare*, met het doel om waarde voor de patiënt te maximaliseren en tegelijkertijd zorgkosten te minimaliseren.²⁴

Het gebruik van deze reeds geregistreerde data zoals declaratiedata voor kwaliteitsanalyses zal in de toekomst toenemen. Een aantal valkuilen moeten hierbij genoemd worden. Bij big data is een goede vraagstelling van tevoren van belang om niet te verdwalen in de hoeveelheid data. Daarnaast is het belangrijk om gezamenlijk met een datamanager en iemand uit het klinisch werkveld een relevante kwaliteitsanalyse te ontwikkelen. Ten slotte is het doen van deze analyses op dit moment nog kostbaar. In toenemende mate wordt ervaring opgedaan over hoe administratieve data gebruikt kan worden voor kwaliteitsanalyses (analyse per patiënt en proces) naast financiële analyses (analyse per procedure en volume), wat mogelijk in de toekomst leidt tot een kostendaling.

Publiceren van data.

In Nederland bestaat bij de beroepsgroep Cardiologie grote terughoudendheid tot publicatie van kwaliteitsdata die te herleiden zijn tot individuele centra of zorgverleners. Bij andere beroepsgroepen in Nederland en in andere landen staat men hier minder negatief tegenover. In Zweden heeft transparantie over de kwaliteit van zorg op basis van uitkomstresultaten bijgedragen aan verhoging van de kwaliteit en een daling van de kosten.²⁵ Zweden, in het bijzonder SWEDEHEART, heeft inmiddels jarenlange ervaring met het publiceren van kwaliteitsdata (voorbeeld in **figuur 2**), waarbij de publieke organisatie van de zorg zorgt voor uniforme criteria en waarbij een specifiek budget bestaat per provincie voor het registreren van de klinische data.²⁶ Sinds 1987 bestaan de Zweedse registraties, waarbij ook de registraties ook worden gebruikt voor het doen van wetenschappelijk onderzoek middels Registry-Randomised Controlled Trials.²⁷ Ook in Nederland zijn meerdere beroepsgroepen waarbij landelijke data worden gebruikt voor het vergelijken van de kwaliteit van zorg. De Nederlandse Vereniging voor Heelkunde heeft het publiceren van landelijke klinische data in Nederland positief ervaren.²⁸ Daarnaast toonde koppeling van klinische data en declaratie data in de colorectale kanker chirurgie aan dat een toename van het aantal complicaties in ziekenhuizen geassocieerd was met een verhoging van de kosten, en vice versa.²⁹

Een belangrijke stap voor het onderling vergelijken van kwaliteit-van-zorg binnen de cardiologie in Nederland is de Nederlandse Hart Registratie, waarbij verschillende klinische registraties in de cardiologie (Meetbaar Beter, NCDR en BHN) zijn samengevoegd en regis-



Figuur 2: Eenjaars-mortaliteit in myocardiinfarct patiënten onder de 80 jaar, uit Zweden in 2015-2016, gepresenteerd per provincie en per ziekenhuis. Bron: Jernberg T. Swedeheart - Annual report 2016. Uppsala, Sweden: Uppsala Clinical Research Center, 2017.³²

treren volgens uniforme criteria. Dit biedt veel potentie voor de koppeling van landelijke registraties met klinische, meer gedetailleerde, informatie.³⁰ De nationale declaratiedata van de verzekeraars, zoals in dit proefschrift, kunnen op wetenschappelijk vlak gebruikt worden voor het genereren van uitkomstdata en het transmuraal vervolgen van de hartinfarct-patiënt. De klinische data vanuit de Nederlandse Hart Registratie kunnen hiermee worden gekoppeld om meer inzicht te krijgen in onderliggende processen en opties tot verbetering. Hierbij speelt de vraag welke klinische variabelen per patiënt relevant zijn om mee te nemen. Een kleine dataset met basiselementen, door de leden van de Nederlandse Vereniging voor Cardiologie bepaald, kan jaarlijks en landelijk worden geregistreerd.

Privacy van de patiënt

Voor de patiënt betekenen de kwaliteitsregistraties een verbetering van de kwaliteit van zorg op populatieniveau en een verbetering in het inzicht in de kwaliteit van zorg van de verschillende instellingen en zorgverleners. Echter speelt bij het gebruik van zorgdata ook het aspect *privacy* van patiëntgegevens in belangrijke mate mee. De eigenaar van de data is aanvankelijk de zorgverlener of instelling, en na overdracht van data aan financiële en / of klinische registraties, is de eigenaar degene die deze registraties beheert en onderhoudt. Zolang data anoniem zijn, zal dit niet interfereren met het recht op privacy van de patiënten en kunnen data eventueel via een Trusted Third Party gekoppeld worden. Ook anonieme data kan herleidbaar zijn tot een patiënt, wanneer een ziekte of behandeling zeldzaam is. Vektis B.V. houdt daarom een grens aan van minimaal 10 patiënten per postcode-gebied wanneer zij hun data delen. De nieuwe wetgeving vanuit Europa (General Data Protection Regulation, GDPR, per 25 mei 2018) is strikter omtrent privacy en vraagt, naast deugdelijke databeveiliging, met name bij het gebruik van kwaliteitsregistraties voor wetenschappelijke doeleinden om goede informed consent en een opt-out regeling.³¹ Dit houdt in dat een patiënt moet weten dat zijn data potentieel gebruikt wordt voor wetenschappelijk onderzoek of kwaliteit-van-zorg analyses welke de volksgezondheid dienen en dat de patiënt te allen tijde de mogelijkheid heeft om zijn of haar gegevens te laten verwijderen uit de databases.

Voor publicatie en het uitwisselen van resultaten van kwaliteits-van-zorg onderzoek, zal de mate van herleidbaarheid van de gebruikte data altijd een discussie blijven. Transparantie van kwaliteit van zorg leidt tot verbetering van de zorg, waarbij het niveau van transparantie afhankelijk is van het onderlinge vertrouwen van de betrokken zorgverleners, instanties en patiënten.

Is onze geboden zorg 'sufficiently safe' ?

Dit proefschrift richtte zich op de vraag hoe je kwaliteit van zorg kan meten om te kijken of de geboden zorg voor de behandeling van acuut coronair syndroom *sufficiently safe* is en deed dit middels twee methoden: lokaal *dossieronderzoek* ten aanzien van patiëntveiligheid (Deel 1) en nationaal *declaratie data-registratie* voor kwaliteit-van-zorg onderzoek (Deel 2). Waar declaratiedata in detail moet inleveren, levert dossieronderzoek in op de efficiëntie. De twee verschillende methodes vullen elkaar aan en dienen een verschillend doel: veiligheid en kwaliteit van zorg.

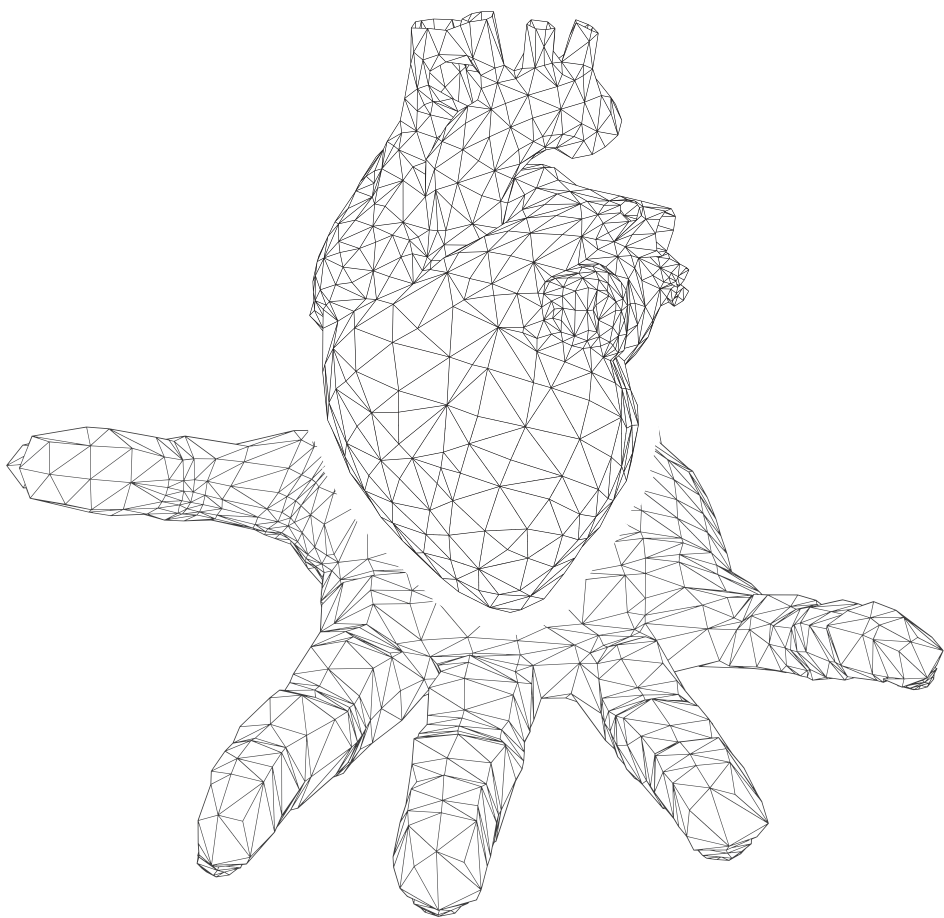
De geboden zorg lijkt veilig, maar toch ervaart 13% zorggerelateerde schade. Meer onderzoek is nodig, maar welk onderzoek? Dossieronderzoek is zeer arbeidsintensief, zelfs een onderzoek binnen het heldere MISSION!-protocol leidt nog tot heterogene antwoorden op causale relaties van zorggerelateerde schade. Real-time monitoring van afwijkende processen met reeds geregistreerde data biedt meer inzicht in zorggerelateerde schade.

De geboden zorg lijkt volgens de richtlijnen te worden gegeven, maar toch krijgt slechts 49% zijn preventieve medicatie. Ook hier is ruimte voor verbetering. Toekomstige analyses met declaratiedata, gecombineerd met klinische data en andere databronnen, kan meer inzicht geven om zo de kwaliteit van zorg continu te blijven verbeteren.

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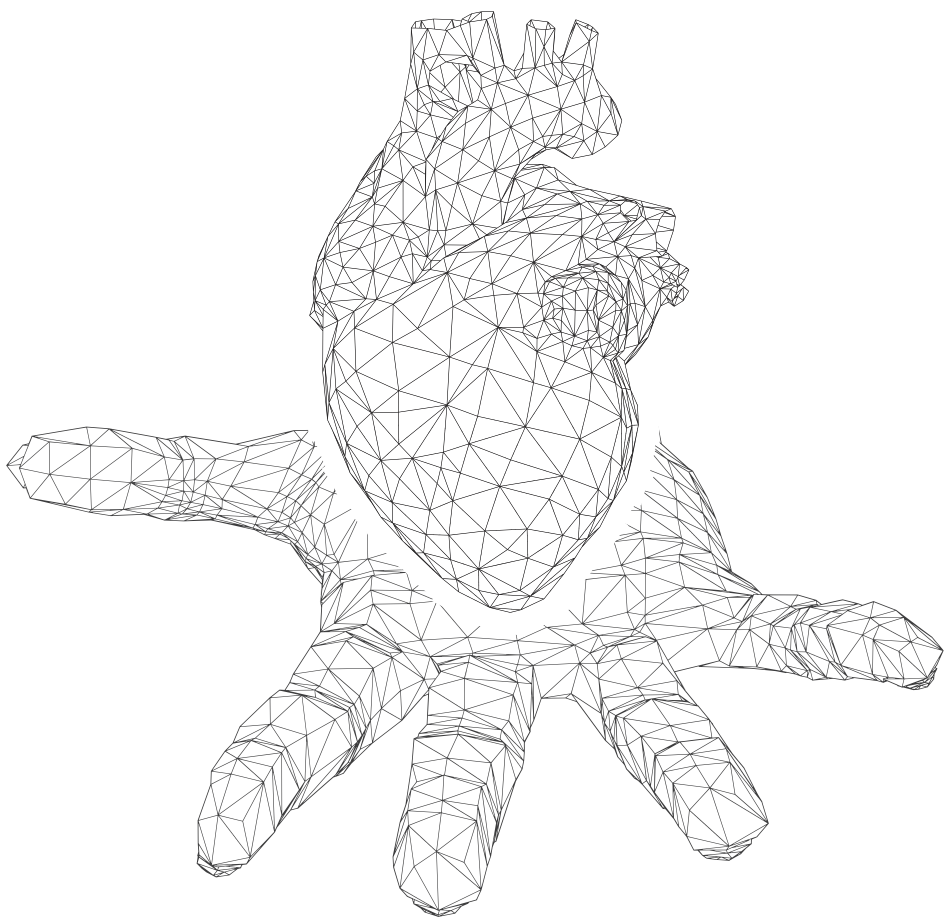
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Abbreviation list

95%-CI	95%-Confidence Interval
ACE-inhibitor	Angiotensin-Converting-Enzyme-inhibitor
ACS	Acute Coronary Syndrome
AE	Adverse Event
AMI	Acute Myocardial Infarction
AT2-inhibitor	Angiotensin-II-inhibitor
ATC	Anatomical Therapeutic Chemical
CAG	Coronary Angiography
CCI	Charlson Comorbidity Index
CK	Creatine Kinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
DDD	Defined Daily Dose
ESC	European Society of Cardiology
GDPR	General Data Protection Regulation
IGZ	Inspectie voor de Gezondheidszorg / Health Care Inspectorate
IOM	Institute of Medicine
KNMG	Koninklijke Nederlandse Maatschappij tot bevordering der Geneeskunst / Royal Dutch Medical Association
LUMC	Leiden University Medical Center
LVEF	Left Ventricular Ejection Fraction
NHR	Nederlandse Hart Registratie / Netherlands Heart Registration
NHS	National Health Service (United Kingdom)
NOAC	Novel oral anticoagulant
NSTEMI	Non-ST-segment Elevation Myocardial Infarction
NVVC	Nederlandse Vereniging voor Cardiologie / Netherlands Society of Cardiology
OR	Odds Ratio
PCI	Percutaneous Coronary Intervention
PD	Process Deviation
SD	Standard Deviation
STEMI	ST-segment Elevation Myocardial Infarction
TTP	Trusted Third Party
UA	Unstable Angina
VKA	Vitamin-K Antagonists
WBP	Wet Bescherming Persoonsgegevens / Protection of Personal Data Act
WGBO	Wet op Geneeskundige Behandeloovereenkomst / Medical Treatment Contract Act
ZN	Zorgverzekeraars Nederland / Collaboration of Healthcare Insurance Companies the Netherlands



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E. van Duijn, N. Reedeker, E.J. Giltay, **D.C. Eindhoven**, R.A. Roos, R.C. van der Mast
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