Adherence to clinical practice guidelines for using invasive coronary angiography in chronic coronary artery disease

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The studies reported in this dissertation were conducted within the project Erfassung und Optimierung der Leitlinienadhärenz im Indikationsstellungsprozess zur Herzkatheteruntersuchung bei stabiler Koronarer Herzerkrankung (ENLIGHT-KHK), which was funded by a grant from the Innovation Committee at the Federal Joint Committee (Gemeinsamer Bundesausschuss (GBA), grant number 01VSF17011).

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Zusammenfassung

Klinische Leitlinien (KL) stellen eine Strategie zur Verringerung von Varianz in der klinischen Versorgung dar und sollen die Anwendung von evidenzbasierten Empfehlungen in der Praxis unterstützen. Leitlinienadhärenz wird als Umsetzung von KL in der Praxis verstanden. Diese kumulative Dissertation untersucht die Leitlinienadhärenz in der Routineversorgung im Bereich des Indikationsstellungsprozesses zur invasiven Koronarangiographie (KA) bei Patient:innen mit chronischer koronarer Herzkrankheit (KHK) in Deutschland. Dies erfolgt anhand von vier Dissertationsprojekten (DP).

DP 1 identifiziert Methoden zur Erfassung der Leitlinienadhärenz bei Leistungserbringer:innen bei chronischer KHK anhand eines Scoping Reviews. In DP 2 wird in einer nationalen prospektiven Beobachtungsstudie (ENLIGHT-KHK) Evidenz zur Leitlinienadhärenz im Indikationsstellungsprozess zur KA bei chronischer KHK generiert. Auf Basis der ENLIGHT-KHK-Studie, führt DP 3 eine Kosten-Effektivitäts-Analyse durch. Dabei werden das Ausmaß der Leitlinienadhärenz und die daraus resultierenden gesundheitsökonomischen Konsequenzen untersucht. Die Anzahl der schwerwiegenden unerwünschten kardialen Ereignisse (MACE) und die Kosten eines vollständig leitliniengerechten KA-Einsatzes (Nationale Versorgungsleitlinie) werden mit dem Status quo in der Routineversorgung verglichen. DP 4 untersucht das Ausmaß der Leitlinienadhärenz nach der deutschen und der europäischen KL bei Patient:innen mit einer Überweisung zur elektiven KA auf Basis von ENLIGHT-KHK.

DP 1 identifiziert Gemeinsamkeiten und Unterschiede bei den verwendeten Methoden zur Erfassung der Leitlinienadhärenz. Hauptschritte der Erfassung wurden identifiziert, und retrospektiv erhobene Sekundärdaten stellten größtenteils die Datengrundlage für die Erfassung dar. Unterschiede lagen bei der Definition der Leitlinienadhärenz, den einzelnen KL-Empfehlungen zugrunde liegenden Evidenz, Auswertung und den Ergebnissen der Leitlinienadhärenz vor. DP 3 zeigt, dass in der Routineversorgung ca. 26 % der KA gemäß den Empfehlungen der Nationalen Versorgungsleitlinie erfolgten. Eine Verbesserung der Leitlinienadhärenz geht mit einer Verringerung der KAs einher. Dabei ist eine vollständig leitliniengerechte verglichen mit dem Status quo der KA-Nutzung mit geringeren Kosten und mit etwas geringeren MACE aus Sicht der gesetzlichen Krankenversicherung (GKV) verbunden. Bei Patient:innen mit einer Überweisung zur KA (DP 4) liegt die Leitlinienadhärenz bei 25,4% nach der deutschen und bei 20,4 % nach der europäischen KL.

Die Ergebnisse dieser Dissertation deuten darauf hin, dass die Umsetzung von Leitlinien im Indikationsstellungsprozess zur KA bei Patient:innen mit chronischer KHK in Deutschland sowohl nach deutschen als auch nach europäischen KL suboptimal ist. Aus gesundheitsökonomischer Sicht würde eine Verbesserung der Leitlinienadhärenz durch (i) eine Reduktion der KAs in der klinischen Praxis und (ii) eine Stärkung der nicht-invasiven bildgebenden Diagnostik zu Kosteneinsparungen und einer leichten Reduktion der MACE aus Sicht der GKV führen.

Eine Verbesserung der Leitlinienadhärenz könnte durch die Implementierung sektorübergreifender Strategien, die aus verschiedenen Komponenten bestehen, erreicht werden. Diese könnten sich insbesondere auf die strukturellen hinderlichen und förderlichen Faktoren bei der Umsetzung von evidenzbasierten Empfehlungen in der Praxis auswirken.

Summary

Clinical practice guidelines (CPG) are proposed as a strategy to reduce practice variation and aim to support the application of evidence-based recommendations in clinical practice. Guideline adherence is understood as the application of CPG in the clinical practice. This cumulative dissertation evaluates the guideline adherence in routine care based on the example of the decision-making process for using invasive coronary angiography (CA) in patients with chronic coronary artery disease (CAD) in Germany. For this purpose, four dissertation projects (DP) are conducted.

DP 1 identifies methods to assess the guideline adherence of health care providers in the care of chronic CA by a scoping review. In DP 2 a prospective observational study (ENLIGHT-KHK) generates evidence on the guideline adherence in patients undergoing a decision-making process for receiving a CA to confirm or exclude an obstructive SCAD. DP 3 conducts a cost-effectiveness analysis based on the ENLIGHT-KHK-trial. The analysis examines the degree of guideline adherence and the corresponding clinical and economic outcomes. Major adverse cardiac events and costs of the complete guideline-adherent use (according to the German National Disease Management Guideline) are compared with those of in the clinical practice observed real-world CA-use. DP 4 examines the degree of guideline adherence according to the German and the European CPG using ENLIGHT-KHK data in patients who were referred to elective CA.

DP 1 identifies similarities and differences in the methods used for assessing guideline adherence. Main steps of assessing guideline adherence were detected, and retrospectively collected secondary data were mostly used as a data source. Differences were detected in the definition of guideline adherence, the evidence underlying the CPG-recommendations, the evaluation and results of guideline adherence. DP 3 shows that in clinical practice ca. 26% of CAs were performed according to the German CPG-recommendations. To improve guideline adherence, a reduction of the amount of CAs in patients with SCAD would be necessary. A guideline-adherent CA-use is less expensive and associated with a slightly lower MACE compared with the observed adherence to CPGs by CA-use in clinical practice for the German Statutory Health Insurance (SHI). In patients referred to CA (DP 4), guideline adherence is 25.4% according to German and 20.4% according to the European CPG.

The findings of this dissertation indicate that the adherence to CPG is suboptimal in the clinical practice of CA-use in patients susceptive of chronic CAD in Germany for both the German and the European CPG. From the health economic perspective, improving adherence to CPG by (i) reducing the amount of CAs and ii) strengthening the role of non-invasive image guided testing modalities would result in cost savings and slightly lower MACE for the German SHI.

To improve guideline adherence, implementation by intersectoral strategies consisting of various components might be promising. Especially, these could affect structural barriers and facilitators when translating evidence-based recommendations into clinical practice.

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List of Abbreviations

CA	Coronary Angiography
CAD	Coronary Artery Disease
cCTA	Coronary Computed Tomography Angiography
CPG	Clinical Practice Guideline
DP	Dissertation Project
DMP	Disease Management Program
eECG	Exercise Electrocardiogram
FFR	Fractional Flow Reserve
ENLIGHT-KHK	Erfassung und Optimierung der Leitlinienadhärenz im Indikationsstellungsprozess zur Herzkatheteruntersuchung bei stabiler Koronarer Herzerkrankung
ESC	European Society of Cardiology
GNDMG	German National Disease Management Guideline
ICD10	International Statistical Classification of Diseases 10th Version
ICER	Incremental Cost-Effectiveness Ratio
MACE	Major Adverse Cardiovascular Events
MPS	Myocardial Perfusion Scintigraphy
PTP	Pre-Test Probability
SCAD	Stable Coronary Artery Disease
SHI	Statutory Health Insurance
Stress-CMR	Stress Cardiac Magnetic Resonance Imaging
Stress-Echo	Stress-Echocardiography

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Chapter 1 Introduction

Over the last few decades, mortality from cardiovascular disease has decreased faster than mortality from other causes due to substantial developments in health care provision[1]. Nevertheless, large variations in care outcomes have been reported both within and across OECD and EU countries, which may be affected by substantial practice variations in healthcare delivery[1,2]. This increasing concern indicates the need to (re) focusing on health care quality[3].

Health care quality is understood as the degree to which health interventions for individuals and populations increase the likelihood of intended health outcomes[4], and is one of the main principles of health policy in OECD and EU countries[3]. Despite different definitions and levels/contexts at which health care quality can be assessed, it encompasses or is part of dimensions which health care is aimed at. These include effectiveness, patient safety, responsiveness/patient-centredness, equity, efficiency, integration and appropriateness of services provided[4–6].

To address questions related to health care quality, clinical guidelines are proposed as a strategy to reduce practice variations by enhancing translating evidence-based recommendations into clinical practice[2,7]. Specifically, clinical practice guidelines (CPG) may help to improve patient outcomes by optimizing the processes of care (e.g. adopting evidence-based therapies)[8–10]. However, the impact of CPG depends on their use (i.e. dissemination and implementation) in clinical practice[2,11]. To understand, appraise or initiate activities to improve the use of CPG in routine practice, knowledge on the extent of their current use in routine care is a prerequisite.

This cumulative dissertation presents how the application of CPG-recommendations in clinical practice can be evaluated in routine care based on the example of a diagnostic process for invasive coronary angiography (CA) in patients with chronic coronary artery disease (CAD) in Germany. For this purpose, the application of CPG was examined by evaluating the guideline adherence which is defined as the *"Conformity in fulfilling or following official, recognized, or institutional requirements, guidelines, recommendations, protocols, pathways, or other standards"*[12]. The evaluation was realized in several phases and included different research elements[13]. First, the methods of assessing guideline adherence were examined, second, a study design, which generated prospective evidence on the degree of guideline adherence was

developed, and, the degree of guideline adherence and the corresponding health economic consequences (i.e. clinical and economic outcomes) were assessed.

This cumulative dissertation consists of ten chapters. Chapter 2 describes the theoretical background, including (i) the medical aspects of chronic CAD and suggested evidence-based care, (ii) the relevance of CPGs, and the link (iii) to guideline adherence, as well as (iii) the rationale and main methods for analysing health economic consequences of guideline adherence. Chapter 3 presents the aim and the specific objectives of the thesis, which are achieved by four dissertation projects (DP) (i.e. peer-reviewed publications). Chapter 4 gives an overview of the methods used. Chapters 5 to 8 present the results by the four DPs, which are discussed in Chapter 9. Finally, Chapter 10 concludes with the main findings from Chapters 5-8 and summarizes insights for future research, policy and practice.

References

1. OECD 2015. Cardiovascular Disease and Diabetes: Policies for Better Health and Quality of Care, OECD Health Policy Studies, OECD Publishing; Paris. http://dx.doi.org/10.1787/9789264233010-en.

2. Panteli D, Legido-Quigley H, Reichebner C, et al. Clinical practice guidelines as a quality strategy. In: Busse R, Klazinga N, Panteli D, et al., editors. Improving healthcare quality in Europe: characteristics, effectiveness and implementation of different strategies. Copenhagen (Denmark): European Observatory on Health Systems and Policies; 2019. (Health Policy Series, No. 53.) 9. https://apps.who.int/iris/handle/10665/327356 p233–263.

3. Busse R, Klazinga N, Panteli D, et al., editors. Improving healthcare quality in Europe: characteristics, effectiveness and implementation of different strategies. Copenhagen (Denmark): European Observatory on Health Systems and Policies, 2019. https://apps.who.int/iris/handle/10665/327356.

4. World Health Organization (WHO) 2023. Quality of care. https://www.who.int/health-topics/quality-of-care (29 September 2023).

5. Institut für Qualitätssicherung und Transparenz im Gesundheitswesen (IQTIG) 2023. Was verstehen wir unter guter Versorgungsqualität? https://iqtig.org/das-iqtig/rahmenbedingungen/wie-definieren-wir-gute-qualitaet/ (29 September 2023).

6. OECD 2017. Caring for Quality in Health: Lessons Learnt from 15 Reviews of Health Care Quality. OECD Reviews of Health Care Quality, OECD Publishing; Paris. https://doi.org/10.1787/22270485.

7. Institute of Medicine 2011. Promoting Adoption of Clinical Practice Guidelines. In: Graham R, Mancher M, Miller Wolman D, et al. editors. Clinical Practice Guidelines We Can Trust. Washington, DC: The National Academies Press. https://doi.org/10.17226/13058 p145–186.

8. Graham R, Mancher M, Miller Wolman D, et al. editors. Institute of Medicine 2011. Clinical Practice Guidelines We Can Trust. Washington, DC: The National Academies Press. https://doi.org/10.17226/13058.

9. Qaseem A, Forland F, Macbeth F, et al., Board of Trustees of the Guidelines International Network. Guidelines International Network: toward international standards for clinical practice guidelines. *Ann Intern Med* 2012;**156**:525–531.

10. Grimshaw JM, Eccles MP, Lavis JN, Hill SJ, Squires JE. Knowledge translation of research findings. *Implement Sci* 2012;**7**:50.

11. Shojania KG, Grimshaw JM. Evidence-based quality improvement: the state of the science. *Health Aff Millwood* 2005;**24**:138–150.

12. Guideline Adherence - MeSH - NCBI https://www.ncbi.nlm.nih.gov/mesh/?term=guideline%20adherence%5BMeSH%20Major%20Topic%5D%29 (29 September 2023).

13. Skivington K, Matthews L, Simpson SA, et al. A new framework for developing and evaluating complex interventions: update of Medical Research Council guidance. *BMJ* 2021;**374**:n2061.

Chapter 2 Theoretical background

2.1. Chronic CAD

2.1.1. Definition

Chronic coronary artery disease (chronic CAD) (i.e. new term 'chronic coronary syndrome'[1]) is characterized by accumulating atherosclerotic plaque in the coronary arteries. Atherosclerotic plaque can narrow the diameter of coronary arteries and may cause an imbalance between the blood supply and demand for oxygen, which can result in myocardial ischemia[2] (i.e. obstructive CAD[3]). Myocardial ischemia can be associated with various symptoms and signs[4], the most manifested as pain or discomfort in the chest. Chest pain (i.e. angina pectoris) is traditionally classified as follows[1,3,4] (Table 1):

Table 1: Classification of chest pain

Typical angina	Meets all three characteristics: (i) Constricting discomfort in the front of the chest or in the neck, jaw, shoulder, or arm; (ii) Precipitated by physical exertion; (iii) Relieved by rest or nitrates within 5 min.
Atypical angina	Meets two of the above characteristics.
Non-anginal chest pain	Meets only one or none of the above characteristics.

Source: Own depiction based on Knuuti et al. 2019[1], Bundesärztekammer et al. 2019[3] and Task Force Members et al. 2013[4].

CAD is a chronic disease with stable periods, but is most often progressive. The disease can be characterized by acute serious events in the further course, i.e. if the plaque is ruptured and leads to an unstable angina pectoris or myocardial infarction. In these scenarios, CAD is not considered chronic and is referred to acute coronary syndrome. [1]

2.1.2. The burden of disease

The prevalence of chronic CAD increases with age and peaks in patients aged ≥65 years[5]. The number of this population at risk increased by 22% (from 16.6 to 18.3 million) between 2011 and 2020 in Germany[6]. Although mortality from chronic CAD has decreased over the last years, chronic CAD represents still the most common cause of death in Germany (75.482 cases in 2020, (International Statistical Classification of Diseases 10th Version (ICD10) I25, chronic

ischaemic heart disease)[6]. Similarly, despite the decline of the number of hospitalized patients[6,7], the hospitalization rate of chronic CAD is still high (ca. 400 per 100.000 persons in 2020). Due to the increasing aging of the population and the associated multimorbidity (e.g. due to diabetes mellitus or obesity), the prevalence of chronic CAD is expected to remain high[6,8].

Economically, the costs of cardiovascular diseases amounted to €56,7 billion (13,1% of €432 billion) in 2020 and represented the highest disease costs in Germany. In particular, the costs for ischemic heart disease (ICD 10, I20-I25 excl. myocardial infarction) for patients aged ≥65 years accounted to €3,5 billion (6%) of the total costs of cardiovascular diseases (€56,7 billion).[9] These costs were estimated from the health system perspective and include costs of prevention, medical treatment, rehabilitation and nursing measures[10].

2.2. Non-invasive testing and invasive coronary angiography

To ensure an appropriate management of chronic CAD-patients (i.e. by lifestyle modification, pharmacological or revascularization therapy), an accurate diagnostic work-up is necessary[1,3,4]. Thereby, either non-invasive testing or CA are available.

2.2.1. Non-invasive testing

After an initial clinical assessment (e.g. of patient's symptoms or history) selecting an appropriate diagnostic test is pivotal[1,3]. For this purpose, various non-invasive testing modalities are available. These are mainly differentiated between functional and anatomical tests[11]. Functional non-invasive testing comprises stress-echocardiography (stress-echo), stress cardiac magnetic resonance imaging (stress-CMR), myocardial perfusion scintigraphy (MPS) or exercise electrocardiogram (eECG)[1,3]. Anatomical non-invasive testing includes the coronary computed tomography angiography (cCTA).[3] While functional non-invasive testing detect inducible myocardial ischemia by consequences of vascular changes, (e.g. electrocardiogram or wall motion abnormalities), anatomical non-invasive testing visualize coronary anatomy (incl. atherosclerotic plaque) and enable detecting stenoses which do not induce myocardial ischemia[1,3,12]. Non-invasive testing with imaging (i.e. visualizing the coronary anatomy) are stress-echo, stress-CMR, MPS and cCTA[3].

2.2.2. Invasive coronary angiography

CA is an invasive procedure for diagnosis of chronic CAD and enables a therapy during the same procedure (i.e. coronary revascularization)[13]. CA aims to visually assess the coronary anatomy and determine the degree of stenosis, plaque or blockage in the coronary artery. CA is considered as a well-established and safe procedure in cardiology[14,15]. Fractional flow reserve (FFR) can supplement a CA allowing to assess the potential of the stenosis to induce myocardial ischemia[14].

Major serious complications such as myocardial infarction, stroke or death occur in <0.1%, and the mild complications such as bleeding or haematoma at the access location occur in ca. 5% of the patients[15]. Although CA is regarded as a low-risk procedure[15], the absolute number of major serious complications is not neglectable[16].

In Germany, approximately 1053 CAs per 100 000 citizens were performed in 2019[17]. At a comparable base-line risk, approximately 690 per 100 000 CAs were conducted in Austria and 600 per 100 000 in Switzerland[18]. For Switzerland, a considerable overuse of inappropriate CAs was concluded[19]. The amount of CAs in Germany has been questioned for several years as being too high compared with other European countries[20–22]. Additionally, it is still unclear whether the regional differences in the amount of conducted CAs reflect the medical needs of the patients[23,24]. The longstanding debate on the amount of CAs raised concerns about potential overuse, especially that of diagnostic CAs in Germany[20].

2.3. Clinical practice guidelines and adherence

The National Academy of Medicine in the US (the former Institute of Medicine) defines CPG as "*statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options"*[25]. This definition was adopted by the German Association of the Scientific Medical Societies (Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften; the AWMF)[26]. CPGs aim to support decision-making of physicians or other health professionals and patients with regard to appropriate health care[25–28].

2.3.1. German National Disease Management Guidelines

In Germany, CPGs are developed by the AWMF and the self-governing bodies of physicians, the German Medical Association (Bundesärztekammer; BÄK) and the National Association of Statutory Health Insurance Physicians (Kassenärztliche Bundesvereinigung; KBV). To promote the integration of health services and to enhance cooperation in cross-sectional and multi-disciplinary health programs (e.g. disease management program (DMP)), the initiative for National Disease Management Guidelines (Nationale VersorgungsLeitlinien; NVL) was established.[29] The NVL-initiative focuses guidelines on highly prevalent chronic diseases (e.g. CAD)[29] and the development is aligned with methods of evidence-based medicine[30].

While different guideline quality levels exist in Germany, the NVL are S3-guidelines which represent the highest methodological level. They incorporate (i) recommendations by experts, (ii) evidence generated and appraised by systematic review methods (e.g. risk-of bias tool), and (iii) a structured consensus process among representative target users (e.g. medical professionals or patients).[30,31] Moreover, S3-guidelines[30] include conclusions on the strength of recommendations for the users which are formulated by a systematic framework (i.e. Grading of Recommendations, Assessment, Development, and Evaluations[32]).

For chronic CAD, the German National Disease Management Guideline (GNDMG) 2019 provides recommendations on prevention, diagnosis and management[3]. Specifically, the diagnostic work-up can be challenging because up to 85% of potentially CAD-attributable symptoms (e.g. chest pain or dyspnoea) are not caused by myocardial ischemia/obstructive CAD[33]. To risk stratify patients, the GNDMG 2019 recommends an algorithmic use of non-invasive testing or CA dependent on the pre-test probability (PTP)[3]. PTP is the probability of CAD given the available information prior to performing a diagnostic test[34]. PTP is estimated based on age, gender and the type of chest pain (e.g. typical chest pain)[33,35,36]. Dependent on the PTP-group, GNDMG 2019 recommends following diagnostic strategies[3]:

(i) PTP <15% (low risk): no testing, other potential causes of symptoms (e.g. gastrointestinal or pulmonary) should be investigated.

(ii) PTP 15–85 (moderate risk): a non-invasive testing such as (a) cCTA), (b) stress-echo, (c) stress-CMR, (d) or MPS. If the non-invasive testing shows a positive result, a CA is recommended in the next step.

(iii) PTP>85% (high risk): a CA without prior non-invasive testing (i.e. direct CA).

Even though the GNDMG 2019 was updated in 2022, the recommendations on diagnostic work-up did not change.

2.3.2. European Society of Cardiology Guidelines

The European Society of Cardiology (ESC) is a medical society which unites national cardiac societies across countries with the aim of providing evidence-based knowledge to cardiovascular professionals by developing and disseminating CPGs[37–39]. The ESC guidelines also impact cardiology in Germany[40], e.g. the German Cardiac Society acknowledges the ESC guidelines in position statements[41]. Moreover, for chronic CAD the PTP-based diagnostic work-up of the GNDMG 2019 is adopted from the guidelines on the management of stable coronary artery disease of the ESC 2013[4]. The current version of the ESC guideline, the ESC Guidelines for the diagnosis and management of chronic coronary syndromes, was updated in 2019[1].

2.3.3. Guideline adherence

The extent of using, adopting or implementing CPG-recommendations in clinical practice refers to guideline adherence[25,28]. National Library of Medicine defines 'guideline adherence' as the *"Conformity in fulfilling or following official, recognized, or institutional requirements, guidelines, recommendations, protocols, pathways, or other standards"* in its Medical Subject Heading database[42].

Guideline adherence can be evaluated for both patients[43,44] or health care providers[45,46]. In the literature on providers' adherence, the terms 'adherence', 'compliance', 'appropriateness' or 'concordance' are used as synonyms[45–51]. The providers' guideline adherence refers to the extent to which health care providers or professionals follow CPGs in the provision of patient health care[52,53].

2.4. Health economic evaluation

2.4.1. Rationale

In addition to evaluating the degree of guideline adherence of CA-use in clinical practice, examining its clinical and economic consequences is a core part of a comprehensive evaluation[28,54]. The effects of choosing one health care service or pathway over another will not only have effects on health outcomes but also on health care resources. These include health professionals or other staff, time of patients and their families, facilities, equipment, consumables or knowledge. For example, resources dedicated to patients with one condition (e.g. CAD) are not available to patients with other conditions (e.g. heart failure), showing that resources are limited which necessitates making choices on their allocation. These allocation decisions are based on various criteria, with some of them explicit (e.g. formal requirements of regulation bodies), others rather implicit (e.g. attitudes).[55]

2.4.2. Model-based cost-effectiveness analysis

To inform allocative decisions, a health economic evaluation provides a framework to evaluate clinical and economic consequences of alternative options[55]. These can refer to 'interventions', 'technologies' or 'care pathways'. Since at least two mutually exclusive alternatives are being considered, the analysis is understood as a comparative health economic evaluation (hereafter 'economic evaluation').[55] Thereby the difference in costs (i.e. incremental costs) is related to the difference in clinical consequences (i.e. incremental effectiveness) between the alternatives and is summarized as the incremental cost-effectiveness ratio (ICER)[55,56]:

$$ICER = \frac{incremental\ costs}{incremental\ effectiveness} = \frac{(costs\ A - costsB)}{(effectivenessA - effectiveness\ B)}$$

While the overall process of estimating costs is similar across most economic evaluations, the nature of clinical consequences resulting from alternatives being evaluated may vary substantially. An economic evaluation where there cost difference is related to a single, natural effect that may differ in the magnitude between the alternatives, is understood as cost-effectiveness analysis. In particular, the unit of effect is often expressed in clinical events such as major adverse cardiovascular events (MACE) avoided. Cost-effectiveness analysis is an appropriate type of economic evaluation for decision contexts where a decision maker, such as

the German Statutory Health Insurance (SHI), is operating with a given budget for a limited range of options within a specific condition.[55]

The cost-effectiveness analysis is conducted by decision analytic modelling (hereafter 'model')[57] which provides a framework to inform decision-making under conditions of uncertainty[58–61]. A model uses mathematical relationships to define a series of possible (health) states or consequences and transitions among these states that would result from alternatives being compared[57]. Based on the inputs into the model (e.g. clinical data), the likelihood of each consequence is expressed in terms of probabilities, and each consequence leads to a cost and an outcome. Consequently, it is possible to calculate the expected costs and outcomes for each alternative under evaluation (by summing up the costs of each consequence weighted by probability of that consequence)[57].

To populate a model with inputs, evidence comes commonly from a range of sources. These could include clinical data (e.g. incidence or baseline risks) from randomised controlled trials or observational studies, and resource use and costs from other sources such as health claims data[55]. However, to ensure appropriate and unbiased model inputs, the process of evidence-gathering should be aligned with principles of evidence-based medicine (e.g. use of systematic review methods)[62]. To illustrate, inputs on treatment effects should be ideally obtained from randomised controlled trials or from a meta-analysis of those.[55]

Different modelling techniques (e.g. decision-tree or Markov) are available and choosing the appropriate one depends on the requirements of the decision problem, e.g. the input data, the patient population and disease, the software, the modellers' expertise and the expected results[63]. For the evaluation, two main concepts can be distinguished in health care modelling: a cohort- and an individual-based approach[64,65].

An individual-based approach model known as 'microsimulation', 'first-order Monte Carlo' or 'individual sampling model' (hereafter 'microsimulation') estimates the health economic outcomes (costs and effects) for individual patients and then the average is calculated across a sufficiently large sample of patients[63,64,66]. In cases where specific patients' characteristics (e.g. gender or risk group) may substantially influence the health economic results, a microsimulation is more preferable.[64,65] For example, if the PTP for CAD impacts the choice of the recommended diagnostic test or therapy option[3].

The purpose of a model-based economic evaluation is not primarily to generate a precise point estimate for a specific outcome (e.g. incremental costs/effects or an ICER) but moreover to systematically examine, and report the uncertainty surrounding this outcome and the decision to be made[57,67–69]. Different concepts relating to uncertainty in decision analytic modeling are distinguished including (i) stochastic (first-order) uncertainty (ii) parameter (second-order) uncertainty and (iii) heterogeneity and (iv) structural uncertainty. These address uncertainty which refers to random variability in patients, estimation of model inputs, and variability between the patients due to specific characteristics or assumptions inherent in the model structure.[67] A key approach to assess uncertainty is the use of sensitivity analysis techniques (e.g. deterministic or probabilistic)[57,67].

References

1. Knuuti J, Wijns W, Saraste A, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J* 2020;**41**:407–477.

2. Gopalan C, Kirk E. Chapter 6 - Coronary artery disease. In: Gopalan C, Kirk E, editors. *Biology of Cardiovascular and Metabolic Diseases*. Academic Press; 2022. p103–122.

3. Bundesärztekammer (BÄK), Kassenärztliche Bundesvereinigung (KBV), Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF) 2019. *National disease management guidelines for chronic CAD (NVL)—long version*, 5th edition. www.khk.versorgungsleitlinien.de (29 September 2023).

4. Task Force Members; Montalescot G, Sechtem U, Achenbach S, *et al.* 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J* 2013;**34**:2949–3003.

5. Wissenschaftliches Institut der AOK (WIdO): Schüssel K, Schlotmann A, Weirauch H, Brückner G, Schröder H, Räker M. *Gesundheitsatlas Deutschland. Koronare Herzkrankheit. Verbreitung in der Bevölkerung Deutschlands: Ursachen, Folgen und Präventionsmöglichkeiten*. Berlin (Germany): WIdO, 2022 https://dx.doi.org/10.4126/FRL01-006434799.

6. Deutsche Herzstiftung 2021. *33. Deutscher Herzbericht 2021*. https://herzstiftung.de/system/files/2022-09/DHB21-Herzbericht-2021.pdf (29 September 2023).

7. Holstiege J, Dammertz L, Kohring C, et al. 2023 *Bundesweite Inzidenztrends diagnostizierter Herzerkrankungen in den Jahren 2013 bis 2021*. 2023.*Versorgungsatlas-Bericht Nr. 23/01*. Berlin: Zentralinstitut für die kassenärztliche Versorgung in Deutschland (Zi). https://doi.org/10.20364/VA-23.01.

8. Khan MA, Hashim MJ, Mustafa H, et al. Global Epidemiology of Ischemic Heart Disease: Results from the Global Burden of Disease Study. *Cureus* 2020; **12**:e9349.

9. Federal Statistics Office (Destatis) 2023. Krankheitskosten: Deutschland, Jahre, Krankheitsdiagnosen https://www.destatis.de/DE/Themen/Gesellschaft-Umwelt/Gesundheit/Krankheitskosten/_inhalt.html#250402 (29 September 2023).

10. Federal Statistics Office Destatis) 2023. Methoden zur Statistik. https://www.destatis.de/DE/Themen/Gesellschaft-Umwelt/Gesundheit/Krankheitskosten/Methoden/_inhalt.html (29 September 2023).

11. Skelly AC, Hashimoto R, Buckley DI, et al. *Noninvasive Testing for Coronary Artery Disease*. Rockville (MD): Agency for Healthcare Research and Quality (US), 2016.

12. Knuuti J, Ballo H, Juarez-Orozco LE, et al. The performance of non-invasive tests to rule-in and rule-out significant coronary artery stenosis in patients with stable angina: a meta-analysis focused on post-test disease probability. *Eur Heart J* 2018;**39**:3322–3330.

13. Discharge Trial Group; Maurovich-Horvat P, Bosserdt M, Kofoed KF, et al. CT or Invasive Coronary Angiography in Stable Chest Pain. *N Engl J Med* 2022;**386**:1591–1602.

14. Hill D, Bykowski A, Lim MJ. Fractional Flow Reserve. In: *StatPearls [Internet]*: Treasure Island (FL). StatPearls Publishing, 2023.

15. Al-Hijji MA, Lennon RJ, Gulati R, et al. Safety and Risk of Major Complications With Diagnostic Cardiac Catheterization. *Circ Cardiovasc Interv* 2019;**12**:e007791.

16. Peper J, Becker LM, Bruning TA, et al. Rationale and design of the iCORONARY trial: improving the cost-effectiveness of coronary artery disease diagnosis. *Neth Heart J* 2023;**31**:150–156.

17. Deutscher Herzbericht 2020. 32. Deutscher Herzbericht. https://herzstiftung.de/system/files/2021-06/Deutscher-Herzbericht-2020.pdf (29 September 2023).

18. Muhlberger V, Kaltenbach L, Bates K, Ulmer H, Austrian National Cardiac Catheterization Laboratory Registry OKG. Cardiac catherization in Austria : Results from the Austrian National Cardiac Catheterization Laboratory Registry (ANCALAR) 2012-2018. *Wien Klin Wochenschr* 2020;**132**:79–89.

19. Chmiel C, Reich O, Signorell A, Tandjung R, Rosemann T, Senn O. Appropriateness of diagnostic coronary angiography as a measure of cardiac ischemia testing in non-emergency patients - a retrospective cross-sectional analysis. *PloS One* 2015;**10**:e0117172.

20. Figulla HR, Lauten A, Maier LS, Sechtem U, Silber S, Thiele H. Percutaneous Coronary Intervention in Stable Coronary Heart Disease -Is Less More? *Dtsch Arztebl Int* 2020;**117**:137–144.

21. Dissmann W, Ridder M de. The soft science of German cardiology. *Lancet* 2002;**359**:2027–2029.

22. Cook S, Walker A, Hügli O, Togni M, Meier B. Percutaneous coronary interventions in Europe: prevalence, numerical estimates, and projections based on data up to 2004. *Clin Res Cardiol* 2007;**96**:375–382.

23. Möckel M, Searle J, Jeschke E. *Indikation, Prognose und regionale Unterschiede der Herzkatheterversorgung in Deutschland*. 1 edn. In: Versorgungs-Report 2013/2014. editors. Klauber J, Günster C, Gerste B, Robra BP and Schmacke N. Stuttgart: Schattauer; 2014, p231–254.

24. Piedmont S, Swart E, Kenmogne R, Braun-Dullaeus RC, Robra BP. [Left-heart catheterization followed by other invasive procedures: Regional comparisons reveal peculiar differences]. *Z Evid Fortbild Qual Gesundhwes* 2017;127–128:62–71.

25. Graham R, Mancher M, Miller Wolman D, et al. editors. Institute of Medicine 2011. *Clinical Practice Guidelines We Can Trust.* Washington, DC: The National Academies Press. https://doi.org/10.17226/13058.

26. Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF) 2023. Leitlinien der AWMF für Ärzt*innen und Gesundheitspersonal | Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e. V. https://www.awmf.org/leitlinien (29 September 2023).

27. World Health Organization (WHO) 2023 Guidelines. https://www.who.int/publications/who-guidelines (29 September 2023).

28. Panteli D, Legido-Quigley H, Reichebner C, et al. Clinical practice guidelines as a quality strategy. In: Busse R, Klazinga N, Panteli D, et al., editors. *Improving healthcare quality in Europe: characteristics, effectiveness and implementation of different strategies.* Copenhagen (Denmark): European Observatory on Health Systems and Policies; 2019. (Health Policy Series, No. 53.) 9. https://apps.who.int/iris/handle/10665/327356 p233–263.

29. Ziele und Grundlagen des NVL-Programms 2023. Leitlinien.de. In: Bundesärztekammer (BÄK), Kassenärztliche Bundesvereinigung (KBV), Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF). *Programm für Nationale VersorgungsLeitlinien – Methodenreport*, 5. Auflage. Version 1. 2017 https://www.leitlinien.de/methodik/5-auflage (29 September 2023).

30. Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF) 2023. Regelwerk | Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e. V. https://www.awmf.org/regelwerk/ (29 September 2023).

31. Schmitt J, Petzold T, Deckert S, Eberlein-Gonska M, Neugebauer EAM. Empfehlungen zur Messung der Versorgungsqualität in aktuellen S3-Leitlinien: Eine kritische Bestandsaufnahme. *Gesundheitswesen* 2014;**76**:819–826.

32. Atkins D, Best D, Briss PA, et al. Grading quality of evidence and strength of recommendations. *BMJ* 2004;**328**:1490.

33. Genders TS, Steyerberg EW, Alkadhi H, et al. A clinical prediction rule for the diagnosis of coronary artery disease: validation, updating, and extension. *Eur Heart J* 2011;**32**:1316–1330.

34. Hunink MGM, Weinstein MC, Wittenberg E et al. Interpreting diagnostic information. In: *Decision Making in Health and Medicine: Integrating Evidence and Values*. Cambridge: Cambridge University Press; 2014, p118-144.

35. Diamond GA, Forrester JS. Analysis of probability as an aid in the clinical diagnosis of coronary-artery disease. *N Engl J Med* 1979;**300**:1350–1358.

36. Juarez-Orozco LE, Saraste A, Capodanno D, et al. Impact of a decreasing pre-test probability on the performance of diagnostic tests for coronary artery disease *Eur Heart J Cardiovasc Imaging* 2019;**20**:1198–1207.

37. European Society of Cardiology (ESC) 2023. Who is the European Society of Cardiology? https://www.escardio.org/The-ESC/Who-we-are, https://www.escardio.org/The-ESC/Who-we-are (29 September 2023).

38. European Society of Cardiology (ESC) 2023. What does the European Society of Cardiology do? https://www.escardio.org/The-ESC/What-we-do (29 September 2023).

39. European Society of Cardiology (ESC) 2022. Clinical Practice Guidelines: Policies and Procedures. https://www.escardio.org/static-file/Escardio/Guidelines/Documents/ESC%20Clinical%20Practice%20Guidelines%20-%20Policies%20and%20Procedures-updated.pdf (29 September 2023).

40. Werdan K. Nationale Versorgungsleitlinie (NVL) Chronische KHK. *Herz* 2016;**41**:537–560.

41. Sechtem U, Achenbach S, Gitt AK, Marx N, Kelm M, Schächinger V. Kommentar zu den 2013 Leitlinien der Europäischen Gesellschaft für Kardiologie (ESC) zum Management der stabilen koronaren Herzkrankheit (KHK). *Kardiologe* 2015;**9**:159–164.

42. Guideline Adherence - MeSH - NCBI https://www.ncbi.nlm.nih.gov/mesh/?term=guideline%20adherence%5BMeSH%20Major%20Topic%5D%29 (29 September 2023).

43. Miller K, Kreis IA, Gannon MR, Medina J, Clements K, Horgan K, Dodwell D, Park MH, Cromwell DA. The association between guideline adherence, age and overall survival among women with non-metastatic breast cancer: A systematic review. *Cancer Treat Rev* 2022;**104**:102353.

44. Farcher R, Graber SM, Thüring N, Blozik E, Huber CA. Does the implementation of an incentive scheme increase adherence to diabetes guidelines? A retrospective cohort study of managed care enrollees. *BMC Health Serv Res* 2023;**23**:707.

45. Gupta S, Mortellaro C, Panda S, et al. Dental implant survival rate in irradiated and non-radiated patients: a systematic review and meta-analysis. *Journal of biological regulators and homeostatic agents* 2021;**35**:53–65.

46. Bulk S van den, Spoelman WA, Dijkman PRM van, Numans ME, Bonten TN, Leiden University Medical Center (LUMC). Non-acute chest pain in primary care; referral rates, communication and guideline adherence: a cohort study using routinely collected health data. *BMC Prim Care* 2022;**23**:336.

47. Labeau SO. Recommendation and protocol compliance: "Yes, I do" may not be true; the complexity of measuring provider adherence. *Intensive Crit Care Nurs* 2020;**60**:102890.

48. Morgan-Hughes G, Williams MC, Loudon M, et al. Downstream testing after CT coronary angiography: time for a rethink? *Open Heart* 2021;**8**:e001597.

49. Leonardi S, Marino M, Crimi G, et al. APpropriAteness of percutaneous Coronary interventions in patients with ischaemic HEart disease in Italy: the APACHE pilot study. *BMJ Open* 2017;**7**:e016909.

50. Rubboli A, La Vecchia L, Casella G, Sangiorgio P, Bracchetti D. Appropriateness of the use of coronary angiography in a population of patients with ischemic heart disease. *Ital Heart J* 2001;**2**:696–701.

51. O'Connor GT, Olmstead EM, Nugent WC, et al. Northern New England Cardiovascular Disease Study Group. Appropriateness of coronary artery bypass graft surgery performed in northern New England. *J Am Coll Cardiol* 2008;**51**:2323–2328.

52. Beidas RS, Mehta T, Atkin M, et al. Dissemination and implementation science: research models and methods in. In: Comer JS, Kendall PC, editors. *The Oxford handbook of research strategies for clinical psychology*. New York: Oxford University Press, 2013, p62–86.

53. Perepletchikova F, Kazdin AE. Treatment Integrity and Therapeutic Change: Issues and Research Recommendations. *Clinical Psychology: Science and Practice* 2005;**12**:365–383.

54. Skivington K, Matthews L, Simpson SA, et al. A new framework for developing and evaluating complex interventions: update of Medical Research Council guidance. *BMJ* 2021;**374**:n2061.

55. Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. *Methods for the Economic Evaluation of Health Care Programmes*. 4th ed. Oxford: Oxford University Press; 2015.

56. Paulden M. Calculating and Interpreting ICERs and Net Benefit. *PharmacoEconomics* 2020;**38**:785–807.

57. Briggs A, Claxton K, Sculpher M. *Decision modelling for health economic evaluation*. Reprint. edn. Oxford: Oxford University Press; 2011.

58. Weinstein MCW, Fineberg HV, Elstein AS et al. *Clinical Decision Analysis*. W.B. Saunders Company 1980.

59. Sox HC, Blatt MA, Higgins MC, Marton KI. *Medical Decision Making*. Boston: Butterworths; 1988.

60. Hunink MGM, Weinstein MC, Wittenberg E et al. *Decision Making in Health and Medicine: Integrating Evidence and Values*. Cambridge: Cambridge University Press; 2014.

61. Brennan A, Akehurst R. Modelling in Health Economic Evaluation. *Pharmacoeconomics* 2000;**17**:445–459.

62. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editors. *Cochrane Handbook for Systematic Reviews of Interventions version 6.3 (updated February 2022)*. Cochrane; 2022. www.training.cochrane.org/handbook.

63. Brennan A, Chick SE, Davies R. A taxonomy of model structures for economic evaluation of health technologies. *Health Econ* 2006;**15**:1295–1310.

64. Davis S, Stevenson M, Tappenden P, Wailoo AJ. The National Institute for Health and Care Excellence (NICE) Decision Support Unit, Technical Support Document 15: cost-effectiveness modelling using patient-level simulation. 2014. https://www.ncbi.nlm.nih.gov/books/NBK310370/ (29 September 2023).

65. Siebert U, Alagoz O, Bayoumi AM, et al. ISPOR-SMDM Modeling Good Research Practices Task Force. State-transition modeling: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--3. *Value Health* 2012;**15**:812–820.

66. Barton P, Bryan S, Robinson S. Modelling in the economic evaluation of health care: selecting the appropriate approach. *J Health Serv Res Policy* 2004;**9**:110–118.

67. Briggs AH, Weinstein MC, Fenwick EA, Karnon J, Sculpher MJ, Paltiel AD. Model parameter estimation and uncertainty analysis: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force Working Group-6. *Med Decis Making* 2012;**32**:722–732.

68. Fenwick E, O'Brien BJ, Briggs A. Cost-effectiveness acceptability curves--facts, fallacies and frequently asked questions. *Health Econ* 2004;**13**:405–415.

69. Maiwenn JAl. Cost-Effectiveness Acceptability Curves Revisited. *PharmacoEconomics* 2013;**31**:93–100.

Chapter 3 Aim and objectives

This cumulative dissertation aimed to evaluate the application of CPG-recommendations in the diagnostic process for CA in routine care in patients with chronic CAD in Germany by assessing the extent of guideline adherence. Following objectives were addressed in four DPs:

DP 1: to examine the methods used for assessing guideline adherence from the perspective of health care providers for invasive procedures in the care of chronic CAD.

DP 2: to provide evidence on the nature and extent of guideline adherence in patients in decision-making process for undergoing CA.

DP 3: to analyse the degree of guideline adherence and the corresponding clinical (i.e. MACE) and economic consequences of CA-use in patients with suspected obstructive SCAD.

DP 4: to examine whether there is a difference in the degree of guideline adherence between the German and European guideline in patients referred for elective CA with suspected obstructive SCAD

Chapter 4 Methods

The DPs (i) the scoping review, (ii) the prospective observational study, (iii) the economic evaluation, and (iv) the subgroup analysis were conducted within the German health services research project 'Erfassung und Optimierung der Leitlinienadhärenz im Indikationsstellungsprozess zur Herzkatheteruntersuchung bei stabiler Koronarer Herzerkrankung' (ENLIGHT-KHK)[1].

4.1. Dissertation project I: Scoping review

A scoping review[2] is a type of knowledge synthesis. It aims to systematically map evidence on a topic and identify main concepts, theories, and knowledge gaps. While systematic reviews are useful for answering clearly defined questions (i.e. patient, intervention, control, and outcome), scoping reviews are useful to answer more broader questions ("What is known about a specific topic"?). Consequently, some methods might be missing (e.g. risk-of-bias assessment)[2]. The scoping review was conducted by systematically searching PubMed and EMBASE in June 2021 (updated in September 2022). Studies were eligible if they (i) assessed guideline adherence among health care providers to evidence-based guidelines for CA or myocardial revascularisation in the health care of chronic CAD, (ii) reported to evaluate guideline adherence as study objective, (iii) described the evaluation methods used and (iv) specified the underlying guidelines and recommendations. Study selection was conducted in duplicate. Data were extracted by two reviewers on study characteristics, methodological aspects such as data sources and variables, definitions of guideline adherence and quantification methods, and the extent of guideline adherence. Additionally, information on the underlying guideline recommendations and the target procedure/population was also extracted. Based on the extracted information, the main steps of assessing guideline adherence were summarized.[3]

4.2. Dissertation project II: Prospective observational study

ENLIGHT-KHK was designed as a multicentre, prospective observational study recruiting 1500 patients being in the decision-making process of using CA for diagnosing or excluding an obstructive SCAD (DRKS00015638). It was set up in hospitals with cardiovascular specialty in the German states North-Rhine Westphalia and Hamburg (2019-2021). The primary outcome measure was the adherence to CPG-recommendations in the decision-making process for CA-

use[1,4]. It was assessed based on the GNDMG "Chronic CAD" 2019[5] and the Guidelines of the ESC on "Diagnosis and management of chronic coronary syndromes" 2019[6]. To determine the patient-level guideline adherence of CA-use[4], patients' PTP for having an obstructive SCAD was examined based on age, gender and the type of chest pain (e.g. typical angina)[7–9]. Non-invasive testing and the results were considered[5,6]. Data were collected from health records in the study sites, health claims data from two German SHIs, and a self-designed patient questionnaire.[4]

4.3. Dissertation project III: Economic evaluation

As part of the ENLIGHT-KHK trial[4], a model-based cost-effectiveness analysis was conducted including recruited patients (n=901)[10]. Using microsimulation [11], the number of MACE and the costs of the real-world CA-use (hereafter 'real-world CA-use') were compared with those of (assumed) complete guideline-adherent use (hereafter 'adherent CA-use')[10]. Guideline-adherent CA-use was based on recommendations of the GNDMG 2019[5]. The microsimulation considered non-invasive testing, CA, revascularization, MACE (30 days after CA), and medical costs (i.e. CA, non-invasive testing, CA-associated MACE). Clinical data inputs were obtained from the ENLIGHT-KHK trial[4] and were based on health records, a standardized patient questionnaire and claims data from the SHI, while costs were based on health claims data only. Incremental cost-effectiveness ratios were calculated by comparing the differences in costs and MACE (i.e. myocardial infarction, stroke, all-cause death) avoided from the perspective of the SHI.[10] To test the robustness of the results, deterministic and probabilistic sensitivity analyses were performed[12].

4.4. Dissertation project IV: Subgroup analysis

In the ENLIGHT-KHK trial, a subgroup of 458 patients with suspected chronic CAD without acute myocardial infarction who referred for elective CA, were recruited in nine German centres (01/2019-08/2021)[13]. Guideline adherence was examined based on the recommendations of the ESC Guideline for the diagnosis and management of chronic coronary syndrome 2019[6] and the GNDMG on chronic coronary artery disease 2019[5]. Thereby, data on the non-invasive testing before CA and the PTP for CAD were collected at patient level using a self-designed patient questionnaire and patients' health records. Non-invasive testing comprised stress-echo, stress-CMR, MPS, cCTA and eECG.[4,13] PTP was determined based on age, gender and the nature of

chest pain (e.g. typical angina, or atypical angina) or dyspnoea[5,6]. Guideline adherence of CA-use was assessed based on the a-priori defined rules. Outcomes measures were analysed by descriptive methods[4,13].

References

1. ENLIGHT-KHK – Erfassung und Optimierung der Leitlinienadhärenz im Indikationsstellungsprozess zur Koronarangiographie bei stabiler Koronarer Herzerkrankung - G-BA Innovationsfonds. https://innovationsfonds.g-ba.de/projekte/versorgungsforschung/enlight-khk-erfassung-und-optimierung-der-leitlinienadhaerenz-im-indikationsstellungsprozess-zur-koronarangiographie-bei-stabiler-koronarer-herzerkrankung.128 (29 September 2023).

2. Tricco AC, Lillie E, Zarin W, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. *Ann Intern Med* 2018;**169**:467–473.

3. Kentenich H, Müller D, Wein B, Stock S, Seleznova Y. Methods for assessing guideline adherence for invasive procedures in the care of chronic coronary artery disease: a scoping review. *BMJ Open* 2023;**13**:e069832.

4. Seleznova Y, Wein B, Muller D, et al. Evaluation of Guideline Adherence for Cardiac Catheterization in Patients With Presumed Obstructive Coronary Artery Disease in Germany (ENLIGHT-KHK) - A Multicentre, Prospective, Observational Study. *Cardiovasc Revasc Med* 2021;**31**:19–25.

5. Bundesärztekammer (BÄK), Kassenärztliche Bundesvereinigung (KBV), Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF) 2019. National disease management guidelines for chronic CAD (NVL)—long version, 5th edition. www.khk.versorgungsleitlinien.de (29 September 2023).

6. Knuuti J, Wijns W, Saraste A, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J* 2020;**41**:407–477.

7. Genders TS, Steyerberg EW, Alkadhi H, et al. A clinical prediction rule for the diagnosis of coronary artery disease: validation, updating, and extension. *Eur Heart J* 2011;**32**:1316–1330.

8. Diamond GA, Forrester JS. Analysis of probability as an aid in the clinical diagnosis of coronary-artery disease. *N Engl J Med* 1979;**300**:1350–1358.

9. Juarez-Orozco LE, Saraste A, Capodanno D, et al. Impact of a decreasing pre-test probability on the performance of diagnostic tests for coronary artery disease *Eur Heart J Cardiovasc Imaging* 2019;**20**:1198–1207.

10. Seleznova Y, Bruder O, Loeser S, et al. Health economic consequences of optimal vs. observed guideline adherence of coronary angiography in patients with suspected obstructive stable coronary artery in Germany: a microsimulation model. *Eur Heart J Qual Care Clin Outcomes* 2023 Mar 9:qcad015.

11. Davis S, Stevenson M, Tappenden P, Wailoo AJ. The National Institute for Health and Care Excellence (NICE) Decision Support Unit, Technical Support Document 15: cost-effectiveness modelling using patient-level simulation. 2014. https://www.ncbi.nlm.nih.gov/books/NBK310370/ (29 September 2023).

12. Briggs A, Claxton K, Sculpher M. *Decision modelling for health economic evaluation*. Reprint. edn. Oxford: Oxford University Press; 2011.

13. Wein B, Seleznova Y, Mueller D, et al. Evaluation of the guideline-adherence of coronary angiography in patients with suspected chronic coronary syndrome – Results from the German prospective multicentre ENLIGHT-KHK project. *Int J Cardiol Heart Vasc* 2023;**46**:101203.

Chapter 5 Dissertation project I: Scoping review

Methods for assessing guideline adherence for invasive procedures in the care of chronic coronary artery disease: a scoping review.

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Abstract

Objectives: In the care of coronary artery disease (CAD), evidence questions the adequate application of guidelines for cardiovascular procedures, particularly coronary angiographies (CA) and myocardial revascularization. This review aims to examine how care providers' guideline adherence for CA and myocardial revascularization in the care of chronic CAD was assessed in the literature.

Design: Scoping review.

Data sources: PubMed and EMBASE were searched through in June 2021 (rerun in September 2022).

Eligibility criteria: We included studies assessing care providers' adherence to evidence-based guidelines for CA or myocardial revascularization in the care of chronic CAD. Studies had to list the evaluation of guideline adherence as study objective, describe the evaluation methods used and report the underlying guidelines and recommendations.

Data extraction and synthesis: Two independent reviewers used standardized forms to extract study characteristics, methodological aspects such as data sources and variables, definitions of guideline adherence and quantification methods, and the extent of guideline adherence. To elucidate the measurement of guideline adherence, the main steps were described.

Results: Twelve studies (311 869 participants) were included, which evaluated guideline adherence by i) defining guideline adherence, ii) specifying the study population, iii) assigning (classes of) recommendations, and iv) quantifying adherence. Thereby, primarily secondary data were used. Studies differed in their definitions of guideline adherence, where six studies each considered only recommendation class I/grade A/strong recommendations as adherent or additionally recommendation classes IIa/IIb. Furthermore, some of the studies reported a priori definitions, and allocation rules for the assignment of recommendation classes. Guideline adherence results ranged from 10% for percutaneous coronary intervention with prior heart team discussion to 98% for coronary artery bypass grafting.

Conclusion: Due to remarkable inconsistencies in the assessment, a cautious interpretation of the guideline adherence results is required. Future efforts should endeavour to establish a consistent understanding of the concept of guideline adherence.

Strengths and limitations of this study

- A robust methodology including a systematic literature search and data extraction conducted in duplicate.

- This review synthesizes the methods used to assess guideline adherence by summarizing the four main steps of guideline adherence measurement.

- Due to the absence of a validated instrument and focusing on examining the methods used to assess guideline adherence, no quality assessment of the methods used to measure guideline adherence could be conducted within this scoping review.

Introduction

Coronary artery disease (CAD) is one of the most important widespread diseases,[1] and still the major cause of mortality at the global level.[2] With a lifetime prevalence of 8%[1] and a proportion of 16% of global deaths,[2] CAD is associated with a significant economic burden for healthcare systems all around the world.[3]

In order to improve the quality of CAD care, which is highly complex and varied in nature, many national and international scientific societies have developed evidence-based clinical practice guidelines.[1,4,5] By systematically providing the best evidence available, these guidelines aim to support health professionals in clinical decision-making and promote high-quality care.[4,6] Furthermore, due to concerns surrounding excessive utilization of tests and procedures, appropriate use criteria (AUCs) have been developed in an effort to improve appropriate resource utilization by providing a consensus judgement on the utility of a test or procedure in specific clinical scenarios. However, AUCs are derivations from the guidelines, and the guidelines remain the primary source of guidance for clinicians.[7]

Although there are established strategies for disseminating and implementing evidence-based guidelines in clinical practice,[8] there is still some question as to whether guidelines for cardiovascular procedures, in particular those for coronary angiography (CA) and myocardial revascularization (e.g. percutaneous coronary intervention (PCI)), are being applied adequately.[9,10]

There has been growing interest recently in evaluating the uptake among healthcare providers of clinical practice guidelines for patient treatment in chronic CAD care, that is, the adherence of healthcare providers to clinical guideline recommendations.[11-14] Since evidence on guideline adherence in clinical practice contributes to quantifying the quality of care[15] and may be used to stimulate activities that promote a more guideline-adherent use of cardiovascular procedures,[14] it is important to ensure that the concept of guideline adherence is measured accurately and consistently. To the best of our knowledge, there is no available evidence on the accuracy and comparability of the methods used to assess guideline adherence for invasive procedures in the field of chronic CAD care. The aim of this scoping review is thus i) to examine the methods and results of studies that assess guideline adherence for invasive diagnostic and

therapeutic procedures in patients with chronic CAD and ii) to compile the general steps used to assess guideline adherence.

Methods

We performed a scoping review of methods used to assess guideline adherence for invasive diagnostic and therapeutic procedures in chronic CAD. The review was reported according to guidance in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews Statement.[16] The review was not registered, and no protocol was published. The study selection process was conducted in duplicate (HK and YS). In case of disagreement, a third reviewer (DM) was consulted. Two reviewers (HK and YS) performed subsequent data extraction using standardized extraction forms.

Literature search

We conducted the search in the bibliographic databases PubMed and EMBASE (via Elsevier) using the search strategies presented in online supplemental file 1. Following removal of duplicates, studies were selected by examining the eligibility criteria stated below. The titles and abstracts were screened, and potentially relevant studies were subjected to a full-text review. In addition to this, cross-references and similar articles from the included articles were checked for inclusion. The search was conducted in June 2021 (and repeated in September 2022).

Eligibility criteria

We selected studies that assessed guideline adherence among healthcare providers for invasive diagnostic or therapeutic procedures in the field of CAD care: CA, PCI and coronary artery bypass grafting (CABG). Guideline adherence was defined as practitioners' decisions following clinical practice guidelines.[14] Thus, in this review, results presented as 'adherent care', 'compliant care',[14] 'care in agreement with the guidelines' and 'appropriate care' were included and summarized under the term 'adherent care'. In order to be considered, the studies had to be published in German or English, list the evaluation of guideline adherence as one of the respective study's objectives, and include a description of the evaluation methods used. In addition to this, the studies had to include patients with chronic CAD and report the corresponding results on guideline adherence. Furthermore, the studies had to list the specific guidelines and recommendations used as a basis for their assessment of adherence. Since

evidence-based guidelines are the primary source of guidance for physicians,[7] the search only included studies that addressed adherence to this type of guidance.

Publications that focused on other decision aids, such as AUCs or performance measures, were excluded because these are derivatives from clinical practice guidelines.[7] Unlike evidence-based guidelines, performance measures aim to operationalise guideline recommendations, whereas AUCs only supplement guideline recommendations using specific clinical scenarios.[7] In addition to this, literature reviews and study protocols were excluded.

Extraction and synthesis of data

Data on the main characteristics of the studies and their results were extracted (for consistency, the results of all the studies are presented in terms of adherence rather than non-adherence). In order to describe the methods used to assess guideline adherence in the field of chronic CAD care, we extracted information relating to the methodological aspects assumed to affect the assessment of guideline adherence,[17] that is, data source and collection, data variables, the study's definition of guideline adherence and the quantification method used. In addition to this, information regarding the underlying guideline recommendations and the target procedure/population was also extracted. Based on these factors, we summarised the main steps used to assess guideline adherence. Since most of data extracted were qualitative in nature, a narrative synthesis was conducted.[18]

Results

Literature search

The search yielded 1384 publications. Following the removal of 252 duplicates, a total of 1132 titles and abstracts were screened and 79 potentially relevant studies were subsequently subjected to a full-text review. Based on the eligibility criteria, 67 of these studies were excluded. As the screening of cross-references and similar articles did not identify any additional relevant publications, 12 studies were ultimately included in this review (see flow chart in Fig. 1 and online supplemental file 2 for details of the excluded studies).

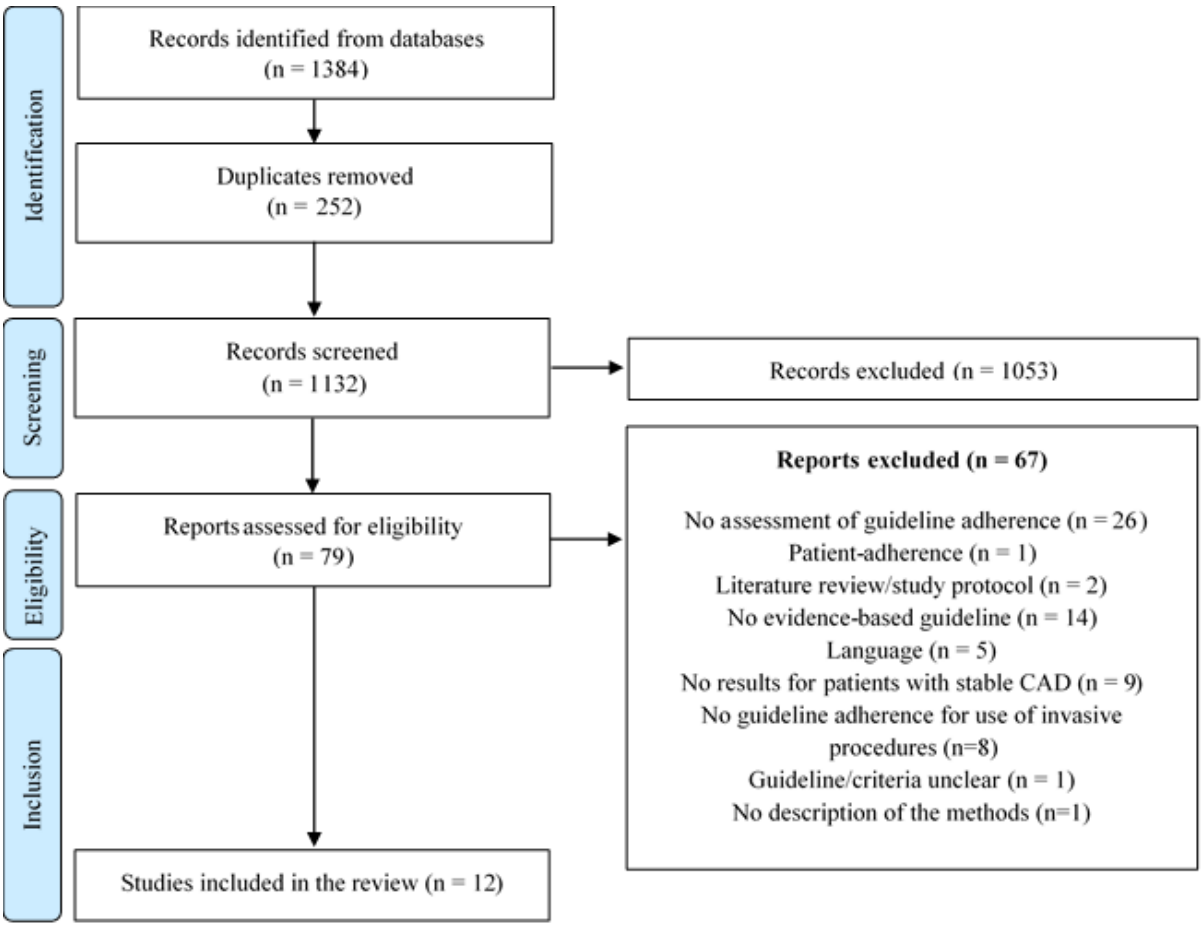

Figure 1: Flowchart for the literature search

Study characteristics

Three of the 12 studies included in the review assessed guideline adherence for the invasive diagnostic CA,[19-21] while nine did so for therapeutic revascularisation by means of a PCI/percutaneous transluminal coronary angioplasty (PTCA) and/or CABG.[22-30] With one exception, all the studies were either based on a retrospective cross-sectional design (n=7)[21,22,25-27,29,30] or a prospective cohort design (n=4).[19,20,24,28] The studies evaluated both primary and specialised care (e.g. catheterisation laboratory) over study periods ranging from 5 months[19] to 5 years[27] during 1991 [22,23] to 2020.[20] The study populations varied with regard to care setting, disease state, prior treatment and patient demographics. An overview of the study characteristics is provided in online supplemental file 3.

Assessment of guideline adherence

Methods and results

The majority of the studies (n=11) evaluated adherence to the guidelines published by the American College of Cardiology (ACC)/the American Heart Association (AHA) and the European Society of Cardiology. Specifically, the studies assessed adherence to recommendations on the performance of a revascularization in general, [23,30] a CABG,[22,24,29] a PCI/PTCA,[22,24,25,27] an ad hoc PCI,[25,26] a PCI with prior heart team discussion [26,28] and a CA.[19-21]

Most of the studies were based on secondary data from registries,[28-30] patient records,[21-26] or administrative data.[22,23,27] However, two studies were based on primary data obtained from prospective records of consecutive patients (e.g. severity of stenosis, symptoms, procedures).[19,20] Eleven of the studies used clinical data variables, including information regarding the extent of CAD, the patients' symptoms, the diagnostic test results, the clinical history, risk factors, and treatments provided.[19-26,28-30] In one study, specific procedure codes and diagnoses within the utilised claims data were resorted.[27]

The studies' definitions of guideline adherence were based on recommendation classes/grades (used in USA, German and European guidelines) or levels of recommendation strengths (used in British guidelines). Recommendation classes/grades or levels of strengths indicate an estimate of the size of treatment effect that takes into account risks and benefits and evidence of and/or agreement on the effectiveness of a procedure.[31,32] In particular, the USA and European guidelines are based on three classes of recommendation: i) class I = procedure is recommended, ii) class II = conflicting evidence/agreement; procedure is reasonable/should be considered (IIa) or may be reasonable/considered (IIb) or iii) class III = procedure is not recommended.[33,34] Similarly, the German guidelines categorise recommendations using three grades: i) grade A = procedure shall (not) be performed, ii) grade B = procedure should (not) be performed or iii) grade 0 = procedure could be performed.[35] In British guidelines, strong recommendations are applied where there is clear evidence of a benefit (i.e. 'offer'), while a less certain recommendation indicates that the evidence of a benefit is less certain (i.e. 'consider').[36]

All the studies determined guideline adherence on an individual basis for each patient and summed it up across the study population. Adherence was quantified using a nominal measure, either binary (adherent/non-adherent treatment),[19,20,23-28,30] multicategorically (useful/justified, uncertain and not useful/not indicated procedures),[21] or a combination of the two.[22,29]

The extent of guideline adherence depended on the procedure in question, and ranged from: 67% to 91% for PCI/PTCA,[22,24,25,27] 17% to 20% for ad hoc PCI,[25,26] 10% to 19% for PCI with prior heart team discussion,[26,28] 49% to 98% for CABG,[22,24,29] 40% to 94% for revascularization in general,[23,30] and 52% to 79% for CA.[19-21] An overview of the methods used to assess guideline adherence is presented in table 1 (for detailed information see online supplemental file 4).

Table 1: Methods

Study	Guideline and treatment decision	Definition of guideline adherence	Quantification and level of measurement
Kiselev et al. 2019 [30]	ESC/EACTS 2014 GL on myocardial revascularization Revascularization	1) Adherence = revascularization if indication 2) Non-adherence = indication without revascularization Indication = class I recommendation	Proportion of adherent/non-adherent treatment A binary measure
Epstein et al. 2003 [23]	ACC/AHA 1988 GL on PTCA ACC/AHA 1991 GL on CABG Revascularization	1) Non-adherence = no revascularization if indication Indication = recommendation class I 2) Non-adherence = revascularization if no indication No indication = class III recommendation	Proportion of non-adherent treatment A binary measure
O'Connor et al. 2008 [29]	ACC/AHA 2004 GL on CABG CABG	Useful procedure = Recommendation class I Evidence favours procedure = Recommendation class IIa Evidence less well established = Recommendation class IIb Procedure not useful = Recommendation class III Adherence = CABG if recommendation class I or II	Proportion of useful, evidence favours procedure, evidence less well established and not useful procedures + adherent and non-adherent to guidelines A multi-categorical and a binary measure
Witberg et al. 2014 [24]	ESC 2010 GL on myocardial revascularization PCI, CABG	Adherence = PCI/CABG according to indication Indication for PCI = recommendation class IIa No indication for PCI/Indication for CABG = recommendation class III for PCI	Proportion of adherent/non-adherent treatment A binary measure
Leape et al. 2003 [22]	ACC/AHA 1988/1993 GL on PTCA ACC/AHA 1991 GL on CABG PTCA, CABG	Justified procedure = recommendation class I Uncertain procedure = recommendation class II No indication for procedure = recommendation class III Adherence= procedures rated as justified and uncertain	Proportion of justified, uncertain, not indicated procedures (and adherent and non-adherent to guidelines) A multi-categorical and a binary measure
Linder et al. 2018 [27]	NVL 2013 on chronic CAD (ESC/EACTS 2014 GL on myocardial revascularization) PCI	Adherence = no PCI if indication for CABG Indication = recommendation grade A (/Class I recommendation for CABG and class III recommendation for PCI)	Proportion of adherent/non-adherent treatment A binary measure

Table 1: Methods

Study	Guideline and treatment decision	Definition of guideline adherence	Quantification and level of measurement
Marino et al. 2020 [25]	ESC/EACTS 2018 GL on myocardial revascularization (ACCF/AHA GL 2012 on stable ischemic heart disease) PCI, Ad hoc PCI	1) Adherence = PCI if strong recommendation for PCI or similar recommendation for PCI/CABG Strong recommendation = Class I recommendation for PCI and class IIb for CABG Similar recommendation = Class I recommendation for PCI and class I for CABG, class IIa recommendation for PCI and class I/II for CABG 2) Non-adherence = ad hoc PCI if indication for heart team discussion Indication = recommendation class I for CABG	Proportion of adherent/non-adherent treatment A binary measure
Leonardi et al. 2017 [26]	ESC 2013 GL on stable CAD ESC/EACTS 2014 GL on myocardial revascularization Ad hoc PCI, PCI with heart team discussion	1) Adherence = heart team discussion if indication 2) Non-adherence = ad hoc PCI if indication for heart team discussion Indication = recommendation class I for heart team, recommendation class I for CABG	Proportion of adherent/non-adherent treatment A binary measure
Yates et al. 2014 [28]	ESC/EACTS 2010 GL on myocardial revascularization PCI with heart team discussion	Adherence = heart team discussion before revascularization if indication Indication = recommendation class I	Proportion of adherent/non-adherent treatment A binary measure
Morgan-Hughes et al. 2021 [20]	NICE CG95 (2016) CA	Non-adherence = Overuse of CA Surrogate: Overuse of CA = CA without strong recommendation and revascularization	Proportion of adherent/non-adherent (overuse of CA) treatment A binary measure
Leung et al. 2007 [19]	ACC/AHA 1999 GL on CA CA	Adherence = CA if recommendation class I or II (Non-adherence = CA if recommendation class III or no recommendation class I or II)	Proportion of adherent/non-adherent treatment A binary measure
Rubboli et al. 2001 [21]	ACC/AHA 1999 GL on CA CA	Adherence = CA if recommendation class I (useful) or IIa (evidence favours procedure) Uncertain = CA if recommendation class IIb (evidence less well established) Non-adherence = CA if recommendation class III (not useful)	Proportion of useful, evidence favours procedure, evidence less well established and not useful procedures + adherent, uncertain and non-adherent procedures A multi-categorical measure

ACC, American College of Cardiology; ACCF, American College of Cardiology Foundation; AHA, American Heart Association; CA, coronary angiography; CABG, coronary artery bypass grafting, CAD, coronary artery disease; ESC, European Society of Cardiology; EACTS, European Association for Cardio-Thoracic Surgery; GL, Guideline; NVL, National disease management guideline; PCI, percutaneous coronary intervention; PTCA, percutaneous transluminal coronary angioplasty.

Main steps used to assess guideline adherence

Four steps for assessing guideline adherence were identified, the first two of which could be undertaken simultaneously (see Fig. 2).

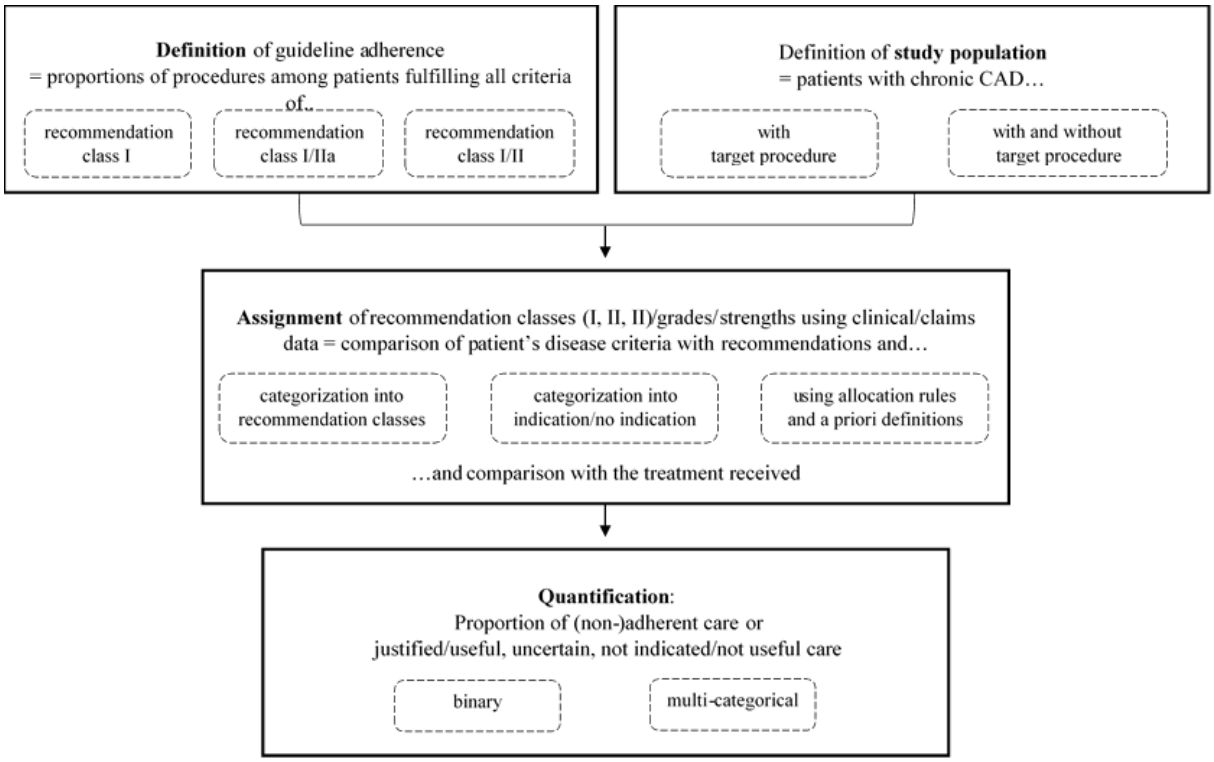

Figure 2: Main steps used to assess guideline adherence

Definition of guideline adherence

In all of the studies, guideline adherence was defined as the proportion of procedures among patients who fulfilled all the criteria for a specific recommendation (class). The recommendations used in the studies varied. Several of the studies limited their definitions of adherent care to procedures corresponding to recommendation class I/grade A/strong recommendations (i.e. 'is recommended'),[20,23,26-28,30] while others additionally considered recommendation class IIa (i.e. 'is probably recommended'),[21,24,25] or even recommendation class IIb (i.e. 'might be considered') [19,22,29] to be adherent.

If the criteria for a specific recommendation (class) were not fulfilled, some of the studies additionally defined guideline-adherent care as 'doing nothing'.[20,23,27,30] Non-adherent care reflected both procedures offered to patients without a corresponding recommendation and cases where no procedure was performed despite revascularisation or diagnostic CA being recommended.

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Definition of study population

While eight of the studies only considered patients who received a specific target procedure,[19,21,22,24-26,28,29] four included patients regardless of what treatment they had received in order to examine guideline adherence for revascularisation or diagnostic CA.[20,23,27,30]

Assignment of recommendations and recommendation classes/grades/strengths

Using clinical data collected from different sources (see Table 1), for each patient it was checked i) which class of recommendation or ii) whether the specific recommendation (class) under evaluation matched the patients' disease criteria (e.g. symptoms, severity of disease). Six of the studies categorised patients into recommendation classes I, II (a,b) and III.[19,21-23,25,29] The remaining studies focused on specific recommendations or recommendation classes (e.g. recommendation class I[30]) and merely categorized patients into two groups: 'procedure indicated' or 'procedure not indicated'.[20,24-28,30] Whether or not the care in question was guideline-adherent was ultimately determined by comparing the results of the assignment with the treatment received. For example, a PCI for a patient with a recommendation class I for PCI was considered adherent.

Overall, there were differences in terms of how the studies dealt with ambiguous assignments and cases of insufficient information for an explicit assignment of recommendation classes. Only one study reported a prespecified allocation rule for cases of an ambiguous assignment (i.e. where a patient was assigned to more than one recommendation class).[27] In cases where guideline criteria had not been explicitly defined, four studies used a priori definitions of these criteria for an explicit assignment (e.g. evidence of ischemia, morbidity risk).[22,23,29,30]

Quantification of guideline adherence

Estimating the proportions of patients with adherent or non-adherent care, nine of the studies used a binary approach.[19,20,23-28,30]

Three of the studies quantified the results according to the considered guidelines using a multicategorical approach, reporting the proportions of procedures within each recommendation class that were defined as justified/useful (class I), uncertain (class II) and not indicated/not useful (class III).[21,22,29] Of these three studies, one adapted this rating to its own

definition by quantifying adherent (class I and IIa), uncertain (class IIb) and non-adherent (class III) procedures.[21] The other two studies used an additional binary categorization into adherent and non-adherent care by accordingly assigning the cases that had initially been classified as uncertain.[22,29]

Discussion

To the best of our knowledge, this is the first scoping review to summarise the methods used to assess guideline adherence in studies that evaluate invasive diagnostic and therapeutic procedures in patients with chronic CAD. Based on 12 studies investigating physicians' adherence to European, USA, German and British guidelines, we examined methods and results and identified the main steps used to assess guideline adherence. The studies included in the review used similar approaches to evaluate guideline adherence, that is, i) defining guideline adherence, ii) specifying the study population, iii) assigning recommendations or recommendation classes/grades/strengths, and iv) quantifying guideline adherence. However, differences were identified with regards to data sources and collection, the definition of guideline adherence, the assignment of recommendation classes/grades/strengths, and the results on guideline adherence.

Data sources and collection

Although two of the studies prospectively collected primary data,[19,20] most used secondary data that had been collected retrospectively.[21-30] Even though secondary data often represent a more easily accessible and affordable data source, they are usually not collected for the purpose of assessing guideline adherence. As a result, the database may be non-specific (i.e. information is available on a more aggregate level without providing clinical details) or incomplete (i.e. required information is missing entirely).[37] This limits the informative value of the database, particularly given the complexity of treatment decisions.

Furthermore, the accuracy of information obtained from patient records, registries and claims data is highly dependent on the standard and quality of the documentation of the care providers.[15,38] In particular, the interpretation and documentation of patients' test results (e.g. extent/significance of coronary stenoses) and symptoms (e.g. type of chest pain), which are key criteria for the assignment of recommendation classes, vary widely.[19,20,24,25,29,39] Moreover, secondary data often fail to provide information on contraindications or patient preferences that

could justify deviations from the guidelines.[22-24] The appropriateness of claims data for assessing guideline adherence might additionally be affected by factors such as the complexity of coding or economic incentives (e.g. coding higher disease severity in order to generate higher payments).[40]

Overall, these issues might have led to misclassification or exclusion of patients and procedures,[15,22,23,26,29,30] and thus contributed to a potential overestimation or underestimation of guideline adherence.[22,23]

A prospective collection of primary data alone or in combination with secondary sources (as reported in two studies [19,20]) may represent the first step towards obtaining a more reliable database. In addition to this, a priori definitions of all variables in order to ensure objective data collection, measures for ensuring data completeness, and methods for handling missing data are requirements for an explicit assignment.

Definition of guideline adherence

Half of the studies only considered recommendation class I/grade A/strong recommendations to be adherent,[20,23,26-28,30] while the others also included recommendation classes IIa and IIb. This difference has a significant impact on the overall results regarding guideline adherence and its interpretation and comparability. For example, excluding recommendation class II would decrease guideline adherence by 11-12% in two of the studies, which assessed CABG [22,29], and by 58% in one study that assessed PCI.[22] The recommendation classes I/strong recommendations[20,22,23,26-28,30] and IIa[21,24,25] are based on high-level evidence, which is associated with a strong or intermediate positive benefit-risk estimate.[7] In contrast, recommendation class IIb as a guideline-adherent scenario[19,22,29] is only associated with a marginal benefit-risk ratio or uncertain outcomes.[7] As such, an assessment of the impact of addressing different classes of recommendation on guideline adherence (e.g. by means of sensitivity analyses) would be appropriate.

Assignment of recommendation classes/grades/strengths

The differences found in the assignment of recommendation classes/grades/strengths relate to the use of a priori definitions of guideline criteria and allocation rules (explicitly assigning each patient to one recommendation (class)). Five of the studies only used these in case of difficulties in the interpretation of guideline criteria or an ambiguous assignment. [22,23,27,29,30] A priori

definitions and allocation rules ensure a more objective and explicit assignment of recommendation classes/grades/strengths. However, different interpretations of assignment criteria and allocation rules in clinical practice and research are likely to affect the measurement of guideline adherence. A consistent understanding of the guideline criteria for clinical implementation and research could be achieved by further establishing the clinical standard criteria developed by the ACC/AHA. The application of these criteria would aim to harmonise cardiovascular terminology, thus enabling improved clinical communication and facilitating research.[41]

Results on guideline adherence

The study results differ in the extent of guideline adherence, particularly between studies that did not examine the same treatment decisions. The lowest extent of adherence was observed for a PCI with prior heart team discussion (10%)[26,28] and an ad hoc PCI (17%),[25] while the highest extent of adherence was observed for CABG (98%).[29] Since a high level of evidence has a positive impact on the implementation of guidelines in clinical practice,[8,22] this variation might be explained by the low level of evidence for the recommendations for PCI with prior heart team discussion and ad hoc PCI (i.e. consensus of experts or small/retrospective studies and registries).[33,42,43] The providers' explanations and the patients' perceptions regarding the benefits and risks of the procedures in question may also contribute to this variation.[44] Patients may frequently request a PCI due to the invasiveness of CABG and the higher value assigned to the short-term benefit of PCI when compared with the long-term advantages of CABG.[44] This might lead to a lower adherence for (ad hoc) PCI.

Those studies that examined the same treatment decision showed less variation than those that evaluated different treatment decisions. The extent of adherence varied least for an ad hoc PCI (between 17% and 20%)[25,26] and most for revascularization in general (between 40% and 94%).[22,24,29] In these studies, the observed variation may be the result of methodological differences (e.g. different data sources or different definitions of guideline adherence).

Guideline adherence may also differ in the time of development and the temporal consistency of guideline recommendations. For example, the lowest extent of guideline adherence was observed for recommendations developed in 2010[24,45] (i.e. heart team discussions before PCI and revascularization decisions based on the Syntax Score [24,26,28]) and for recommendations that changed significantly over time [46] (ad hoc PCI[26]). This might indicate difficulties in the

implementation of the evolving and more complex recommendations over the wide time span evaluated into practice.[8] However, the heterogeneity of the included studies did not allow an analysis of a temporal trend.

Furthermore, the variation of results may be influenced by external factors.[8] For example, initiatives to improve the quality and cost-effectiveness of care using decision aids (e.g. AUCs and performance measures) and financial incentives to encourage compliance with guidelines (e.g. pay-for-performance models) are well established in the United States,[7,47] and may have improved awareness of clinical guidelines among providers.[48]

In addition, guideline adherence results vary in terms of the interpretation of non-adherence. Because in most of the studies only the proportion of patients receiving a procedure without a corresponding indication was reported, the derived non-adherence could be primarily interpreted as potential overuse. However, both overuse and underuse of medical procedures reduce quality of care.[49] Therefore, to assess the proportion of patients not receiving a procedure with an indication (as reported in two studies [23,30]) would also be informative for developing targeted interventions to promote high quality care.

Some efforts will be needed in order to advance research on guideline adherence and improve the credibility of the results. First, prospective databases that comply with guideline criteria should be developed for an objective collection of relevant clinical data. Second, the establishment and use of consistent definitions for guideline criteria (eg, the clinical standard criteria published by the ACC/AHA) should be promoted in care and research. Third, in order to facilitate an adequate interpretation of results, we highly recommend the development of reporting standards for studies that evaluate guideline adherence.

Limitations

This review should be interpreted in the context of the following limitations. First, the literature search was performed in two databases and was limited to studies available in German or English, so other studies relevant to the review may have been overlooked. However, this may only have a minor impact on the results of this review, as the screening of the reference lists of the studies included in the search did not yield additional methods.

Second, due to the absence of a validated instrument, it was not possible to conduct a quality assessment of the methods used to measure guideline adherence. However, since the primary

objective of this review was to examine the methods used to assess guideline adherence, this might likely not affect the results of this review.

Third, most of the included studies were retrospective in design and used secondary data, so the credibility of the guideline adherence results is limited. However, we extensively discussed these methodological aspects among others to enable readers to adequately interpret results on guideline adherence.

Conclusion

We observed inconsistencies in the assessment that limit the credibility and comparability of the guideline adherence results. For researchers, the four assessment steps identified in the review may serve as orientation for ensuring consistency. However, the data collection, the definitions, the assignments of recommendations and the methods of quantification require further standardisation. Since evidence on guideline adherence may be used to set up tailored interventions in clinical practice patterns in efforts to improve care, the available evidence regarding guideline adherence should be interpreted with caution. As such, future efforts should endeavour to establish a consistent understanding of the concept of guideline adherence.

Contributors: HK, YS and DM were involved in the conception and design of this review. The selection of articles was carried out by HK and YS, consulting DM as third reviewer in case of disagreement. The data extraction and analysis were conducted and guided by HK and YS. All the authors contributed to the data interpretation. HK and YS wrote the final manuscript. BW, DM and SS critically revised the final manuscript. All the authors read and approved the final manuscript. YS is responsible for the overall content as guarantor.

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References

1. Bundesärztekammer (BÄK), Kassenärztliche Bundesvereinigung (KBV), Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF) 2019. National disease management guidelines for chronic CAD (NVL)—long version, 5th edition. www.khk.versorgungsleitlinien.de (29 September 2023).

2. World Health Organization. The top 10 causes of death. 2020. www.who.int/news-room/fact-sheets/detail/the-top-10- causes-of-death (4 January 2022).

3. Bauersachs R, Zeymer U, Brière JB, Marre C, Bowrin K, Huelsebeck M. Burden of coronary artery disease and peripheral artery disease: a literature review. *Cardiovasc Ther* 2019;**2019**:8295054.

4. Graham R, Mancher M, Miller Wolman D, et al. editors. Institute of Medicine 2011. Clinical Practice Guidelines We Can Trust. Washington, DC: The National Academies Press. https://doi.org/10.17226/13058.

5. Knuuti J, Wijns W, Saraste A, et al. 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J* 2020;**41**:407–477.

6. The Cochrane Collaboration. Leitlinien | cochrane deutschland. 2022. www.cochrane.de/de/leitlinien (5 April 2022).

7. Jacobs AK, Anderson JL, Halperin JL, et al. The evolution and future of ACC/AHA clinical practice guidelines: a 30-year journey: a report of the American College of Cardiology/American Heart Association task force on practice guidelines. *Circulation* 2014;**130**:1208–1217.

8. Fischer F, Lange K, Klose K, Greiner W, Kraemer A. Barriers and strategies in guideline implementation-a scoping review. *Healthcare (Basel*) 2016;**4**:36.

9. Hannan EL, Racz MJ, Gold J, et al. Adherence of catheterization laboratory cardiologists to American College of Cardiology/American Heart Association guidelines for percutaneous coronary interventions and coronary artery bypass graft surgery: what happens in actual practice? *Circulation* 2010;**121**:267–275.

10. Chmiel C, Reich O, Signorell A, Tandjung R, Rosemann T, Senn O. Appropriateness of diagnostic coronary angiography as a measure of cardiac ischemia testing in non-emergency patients - a retrospective cross-sectional analysis. *PLoS One* 2015;**10**:e0117172.

11. Beckmann A, Bitzer E-M, Lederle M, et al. Health care analysis on myocardial revascularization in patients with chronic coronary artery disease: the multicenter REVASK study: design and protocol. *Thorac Cardiovasc Surg* 2021;**69**:599–606.

12. Seleznova Y, Wein B, Müller D, et al. Evaluation of guideline adherence for cardiac catheterization in patients with presumed obstructive coronary artery disease in germany (ENLIGHT-KHK) – A multicentre, prospective, observational study. *Cardiovas Revasc Med* 2021;**31**:19–25.

13. Beidas RS, Mehta T, Atkin M, et al. Dissemination and implementation science: research models and methods in. In: Comer JS, Kendall PC, editors. *The Oxford handbook of research strategies for clinical psychology*. New York: Oxford University Press, 2013, p62–86.

14. Labeau SO. Recommendation and protocol compliance: " yes, I do" may not be true; the complexity of measuring provider adherence. *Intensive Crit Care Nurs* 2020;**60**:102890.

15. Milchak JL, Carter BL, James PA, Ardery G. Measuring adherence to practice guidelines for the management of hypertension: an evaluation of the literature. *Hypertension* 2004;**44**:602–608.

16. Tricco AC, Lillie E, Zarin W, et al. PRISMA extension for scoping reviews (PRISMA-scr): checklist and explanation. *Ann Intern Med* 2018;**169**:467–473.

17. Popay J, Roberts H, Sowden A, et al. 2006. Guidance on the conduct of narrative synthesis in systematic reviews: a product from the ESRC methods programme. https://www.lancaster.ac.uk/media/lancaster-university/content-assets/documents/fhm/dhr/chir/NSsynthesisguidanceVersion1-April2006.pdf.

18. Campbell M, McKenzie JE, Sowden A, et al. Synthesis without meta-analysis (SWiM) in systematic reviews: reporting guideline. *BMJ* 2020;**368**:l6890.

19. Leung DY, Hallani H, Lo ST, Hopkins AP, Juergens CP. How compliant are we with guidelines for coronary angiography in clinical practice? *Intern Med J* 2007;**37**:699–704.

20. Morgan-Hughes G, Williams MC, Loudon M, et al. Downstream testing after CT coronary angiography: time for a rethink? *Open Heart* 2021;**8**:e001597.

21. Rubboli A, La Vecchia L, Casella G, Sangiorgio P, Bracchetti D. Appropriateness of the use of coronary angiography in a population of patients with ischemic heart disease. *Ital Heart J* 2001;**2**:696–701.

22. Leape LL, Weissman JS, Schneider EC, Piana RN, Gatsonis C, Epstein AM. Adherence to practice guidelines: the role of specialty society guidelines. *Am Heart J* 2003;**145**:19–26.

23. Epstein AM, Weissman JS, Schneider EC, Gatsonis C, Leape LL, Piana RN. Race and gender disparities in rates of cardiac revascularization: do they reflect appropriate use of procedures or problems in quality of care? *Med Care* 2003;**41**:1240–1255.

24. Witberg G, Lavi I, Gonen O, et al. Long-Term outcomes of patients with complex coronary artery disease according to agreement between the SYNTAX score and revascularization procedure in contemporary practice. *Coron Artery Dis* 2014;**25**:296–303.

25. Marino M, Leonardi S, Crimi G, et al. Lack of implementation of guidelines recommendations for coronary revascularization in stable patients with complex disease is associated with high rates of incomplete revascularization: analysis from the APACHE study. *Heart Vessels* 2020;**35:**30–37.

26. Leonardi S, Marino M, Crimi G, et al. Appropriateness of percutaneous coronary interventions in patients with ischaemic heart disease in Italy: the APACHE pilot study. *BMJ Open* 2017;**7**:e016909.

27. Linder R, Zeidler J, Verheyen F, von der Schulenburg JG, Haverich A, Schilling T. Guidelines versus reality: is coronary stent application in three-vessel disease standard or the exception? *Eur J Health Econ* 2018;**19**:821–830.

28. Yates MT, Soppa GK, Valencia O, Jones S, Firoozi S, Jahangiri M. Impact of European society of cardiology and european association for cardiothoracic surgery guidelines on myocardial revascularization on the activity of percutaneous coronary intervention and coronary artery bypass graft surgery for stable coronary artery disease. *J Thorac Cardiovasc Surg* 2014;**147**:606–610.

29. O'Connor GT, Olmstead EM, Nugent WC, et al. Appropriateness of coronary artery bypass graft surgery performed in Northern New England. *J Am Coll Cardiol* 2008;**51**:2323–2328.

30. Kiselev AR, Korotin AS, Posnenkova OM, Popova YV, Prokhorov MD, Gridnev VI. Discrepancy between the European clinical guidelines and myocardial revascularization in patients with stable coronary artery disease in Russia. *Int J Qual Health Care* 2019;**31**:269–275.

31. Hillis LD, Smith PK, Anderson JL, et al. 2011 ACCF/AHA guideline for coronary artery bypass graft surgery: a report of the American College of Cardiology Foundation/American Heart Association Task force on practice guidelines. *Circulation* 2011;**124**:e652–735.

32. NICE. Making decisions using NICE guidelines 2021. www. nice.org.uk/about/what-we-do/our-programmes/nice-guidance/niceguidelines/ making-decisions-using-nice-guidelines (20 December 2021).

33. Developed with the special contribution of the European Association for Percutaneous Cardiovascular Interventions (EAPCI), Authors/ Task Force Members, Wijns W, et al. Guidelines on myocardial revascularization: the task force on myocardial revascularization of the European Society of cardiology (ESC) and the European association for cardio-thoracic surgery (EACTS). *Eur Heart J* 2010;**31**:2501–2555.

34. American College of Cardiology Foundation and American Heart Association. Methodology manual and policies from the ACCF/AHA task force on practice guidelines. 2010. www.acc.org/ guidelines/about-guidelines-and-clinical-documents/methodology (20 December 2021).

35. Bundesärztekammer (BÄK), Kassenärztliche Bundesvereinigung (KBV), Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF). Programm für nationale versorgungsleitlinien – methodenreport, 5. Auflage. version 1. 2017. Available: www.leitlinien.de/methodik (8 June 2022).

36. NICE. Developing NICE guidelines: the manual. 9 writing the guideline. 2014. www.nice.org.uk/process/pmg20/chapter/ writing-the-guideline (12 April 2022).

37. Boslaugh S. *Secondary data sources for public health: a practical guide*. Cambridge: Cambridge University Press, 2007.

38. Chan KS, Fowles JB, Weiner JP. Review: electronic health records and the reliability and validity of quality measures: a review of the literature. *Med Care Res Rev* 2010;**67**:503–527.

39. Patel MR, Bailey SR, Bonow RO, et al. ACCF/SCAI/AATS/AHA/ ASE/ASNC/HFSA/HRS/SCCM/SCCT/SCMR/STS 2012 appropriate use criteria for diagnostic catheterization: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, Society for Cardiovascular Angiography and Interventions, American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society of Critical Care Medicine, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, and Society of Thoracic Surgeons. *J Am Coll Cardiol* 2012;**59**:1995–2027.

40. Swart E, Ihle P, Gothe H, Matusiewicz D. *Routinedaten im Gesundheitswesen. Handbuch Sekundärdatenanalyse: Grundlagen, Methoden und Perspektiven*. Bern: Verlag Hans Huber, Hogrefe AG, 2014.

41. Hendel RC, Bozkurt B, Fonarow GC, et al. ACC/AHA 2013 methodology for developing clinical data standards: a report of the American College of Cardiology/american Heart Association task force on clinical data standards. *J Am Coll Cardiol* 2014;**63**:2323–2334.

42. Task Force Members, Montalescot G, Sechtem U, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the task force on the management of stable coronary artery disease of the European Society of cardiology. *Eur Heart J* 2013;**34**:2949–3003.

43. Authors/Task Force members, Windecker S, Kolh P, et al. 2014 ESC/ EACTS guidelines on myocardial revascularization: the task force on myocardial revascularization of the European Society of cardiology (ESC) and the European association for cardio-thoracic surgery (EACTS) developed with the special contribution of the European association of percutaneous cardiovascular interventions (EAPCI). *Eur Heart J* 2014;**35**:2541–2619.

44. Osnabrugge RL, Head SJ, Bogers AJ, Kappetein AP. Appropriate coronary artery bypass grafting use in the percutaneous coronary intervention era: are we finally making progress? *Semin Thorac Cardiovasc Surg* 2012;**24**:241–243.

45. Young MN, Kolte D, Cadigan ME, et al. Multidisciplinary heart team approach for complex coronary artery disease: single center clinical presentation. *J Am Heart Assoc* 2020;**9**:e014738.

46. Blankenship JC, Gigliotti OS, Feldman DN, et al. Ad hoc percutaneous coronary intervention: a consensus statement from the society for cardiovascular angiography and interventions. *Catheter Cardiovasc Interv* 2013;**81**:748–758.

47. Kahn JM, Scales DC, Au DH, et al. An official American thoracic Society policy statement: pay-for-performance in pulmonary, critical care, and sleep medicine. *Am J Respir Crit Care Med* 2010;**181**:752–761.

48. Uchmanowicz I, Hoes A, Perk J, *et al*. Optimising implementation of European guidelines on cardiovascular disease prevention in clinical practice: what is needed? *Eur J Prev Cardiol* 2021;**28**:426–431.

49. Saini V, Brownlee S, Elshaug AG, Glasziou P, Heath I. Addressing overuse and underuse around the world. *Lancet* 2017;**390**:105–107.

Chapter 6 Dissertation project II: Prospective observational study

Evaluation of guideline adherence for cardiac catheterization in patients with presumed obstructive coronary artery disease in Germany (ENLIGHT-KHK) – A multicentre, prospective, observational study.

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Abstract

Introduction: The diagnosis or exclusion of obstructive stable coronary artery disease (SCAD) in clinical practice is challenging and therefore clinical guidelines provide recommendations on the use of non-invasive and invasive testing. For Germany, data obtained from the OECD and health insurances indicate a potential non-adherence to guideline-recommended diagnostic pathways. However, there is a lack of prospective and reliable evidence for appropriate use for invasive coronary angiography (CA) in Germany.

Objective: To provide evidence on the nature and extent of guideline non-adherence in patients undergoing CA with presumed obstructive SCAD in Germany and, to evaluate the clinical and economic consequences of potential deviations in guideline adherence.

Methods: ENLIGHT-KHK is a multicentre, prospective observational study recruiting 1,500 patients being admitted for CA with presumed obstructive SCAD and exclusion of acute myocardial infarction (DRKS00015638**)**. The primary outcome measure is the adherence to clinical guidelines in the decision-making process for use of CA. Therefore, the patients' diagnostic pathways and adherence to German and European guidelines will be assessed using clinical data, health-claims data, and a patient questionnaire. The primary safety outcome is a composite of myocardial infarction, stroke and all-cause death. Secondary outcome measures are periprocedural complications and costs. Using a decision-analytic model, the clinical and economic impact of observed guideline adherence in clinical practice will be assessed. Potential barriers and facilitators of guideline-adherent decision-making will be evaluated via semi-structured interviews.

Conclusions: ENLIGHT-KHK will give insights into the appropriateness of invasive CA in Germany and enable the development of concepts to improve guideline-adherence in the German health-care setting.

The content of dissertation project II has been published in Cardiovasc Revasc Med

Keywords: Coronary artery disease; diagnosis; coronary angiography; economic evaluation; guideline; adherence

Abbreviations: CA, Coronary Angiography; CABG, Coronary Artery Bypass Grafting; CAD, Coronary Artery Disease; CCS, Canadian Cardiovascular Society; cCTA, Coronary Computed Tomography Angiography; cMRI, Cardiac Magnetic Resonance Imaging; EBM, German Uniform Assessment Standard ("Einheitlicher Bewertungsmaßstab"); eCRF, Electronic Case Report Form; ED, Emergency Department; ESC, European Society of Cardiology; G-DRG, German Diagnosis-Related Groups. ICD, International Statistical Classification of Diseases (10th Version); ICH-GCP, International Conference on Harmonisation-Good Clinical Practice; MACE, Major Adverse Cardiovascular Events; OPS, German Procedure Classification ("Operationen- und Prozedurenschlüssel"); PCI, Percutaneous Coronary Intervention; PTP, Pre-test Probability; SCAD, Stable Coronary Artery Disease; SHI, Statutory Health Insurance.

Introduction

Coronary artery disease (CAD) is associated with a high prevalence, incidence, morbidity, and mortality in industrialised countries and contributes significantly to healthcare expenditures[1, 2]. Diagnosing obstructive stable CAD (SCAD) can be challenging as – depending on age, gender and clinical symptoms – non-ischemic causes are more or less likely. Therefore, various diagnostic and therapeutic strategies are indicated[3,4]. To provide an evidence-based decision support in clinical practice, recently published European and German disease management guidelines recommend a risk-stratified approach with the use of non-invasive testing in the majority of patients. According to these guidelines, invasive testing with coronary angiography (CA) is only recommended in patients with a high likelihood of ischemia during non-invasive testing[3,5]. The recently published European Society of Cardiology (ESC) Guidelines on the diagnosis and management of the chronic coronary syndrome further strengthened the role of non-invasive testing with imaging (e.g. stress-echocardiography, coronary computed tomography -angiography (cCTA), or cardiac magnetic resonance imaging (cMRI)) against invasive CA[3].

In Germany, despite the strong recommendations for non-invasive testing (Class I 'is recommended')[5], about 1 125 CA and nearly 400 percutaneous coronary interventions (PCI) per 100 000 citizens are performed per year, 1.7 times more than second-placed Austria[6,7]. In addition to observed significant interregional variations in the use of invasive testing[8-10], these analyses indicate at least partial non-adherence to clinical guidelines and a potential overuse of CA. Evidence from the United States suggests that improving adherence to guideline recommendations may increase a resource-efficient use of diagnostic techniques[11,12]. Despite the clinical and health-economic relevance[13,14], to date there are no prospective data on the nature and extent of guideline-adherence in the use of CA in patients with suspected obstructive SCAD in Germany[6,15].

ENLIGHT-KHK will prospectively analyse the potential non-adherence to clinical guideline recommendations and its clinical and economic implications. Further, this trial will facilitate developing recommendations to ensure a guideline-oriented and resource-efficient provision of non-invasive and invasive testing.

The primary objectives are:

1. to map the indication process for CA in patients at risk for obstructive SCAD and to assess the degree of potential guideline deviations and

2. to assess the occurrence of major adverse cardiovascular events (MACE) as a composite of myocardial infarction, stroke, and all-cause death after CA in clinical practice.

The secondary objectives are:

- to compare the clinical outcomes (i.e. MACE) and costs of the observed clinical practice with an assumed complete guideline-adherent process,
- to analyse the barriers and facilitators of a guideline-adherent indication and
- to provide prospective evidence for developing recommendations which should stimulate a resource-efficient and guideline-based care for patients at risk for obstructive SCAD in Germany.

Methods

Study design and setting

ENLIGHT-KHK is designed as a multicentre, prospective observational study which is set up in hospitals with cardio-vascular specialty (July 2020: n=7) in the German states North-Rhine Westphalia and Hamburg. Enrolment of the planned 1 500 patients takes place from January 2019 to June 2021. The study is registered at DRKS - German Clinical Trials Register on 19th February 2019 under the identifier DRKS00015638.

Patient population and recruitment

Generally, subjects are eligible for enrolment if they are ≥18 years old, provide written informed consent, and are insured at one of the participating statutory health insurances (SHI) (i.e. AOK Rheinland/Hamburg and AOK NORDWEST, respectively).

To analyse the adherence to clinical guidelines in the decision-making process of using CA for diagnosing or excluding an obstructive SCAD, patients are included if they a) are suspected to have an obstructive SCAD without acute coronary syndrome and b) are assigned to or did receive a CA within the current admission. To exploratively assess the broader scope of the clinical decision practice, subjects are also included in three secondary cohorts if they are c) referred to outpatient cardiologic consultation for potentially ischemia-driven symptoms, d) hospitalized or self-referred to an emergency department (ED), chest pain unit, or normal ward for exclusively non-invasive testing, or e) referred to non-invasive image testing with cCTA, stress-echocardiography or cMRI.

Subjects are excluded if they have an acute coronary syndrome, cardiogenic shock, a diagnostic CA before open heart surgery or for the diagnostic evaluation of heart failure.

Patients who meet the eligibility criteria are invited to participate in ENLIGHT-KHK. After providing written informed consent, patients are asked to complete a standardized questionnaire addressing symptoms, exercise tolerance, and healthcare utilization prior to inclusion. Furthermore, documented clinical data and data on the process of establishing the indication for CA are collected from the patients' medical records. To assess the health utilization pathways and costs, claims data are provided by the participating SHI for each patient from 6 months prior to 3 months after inclusion[16,17]. Figure 1 shows the patients' inclusion flow.

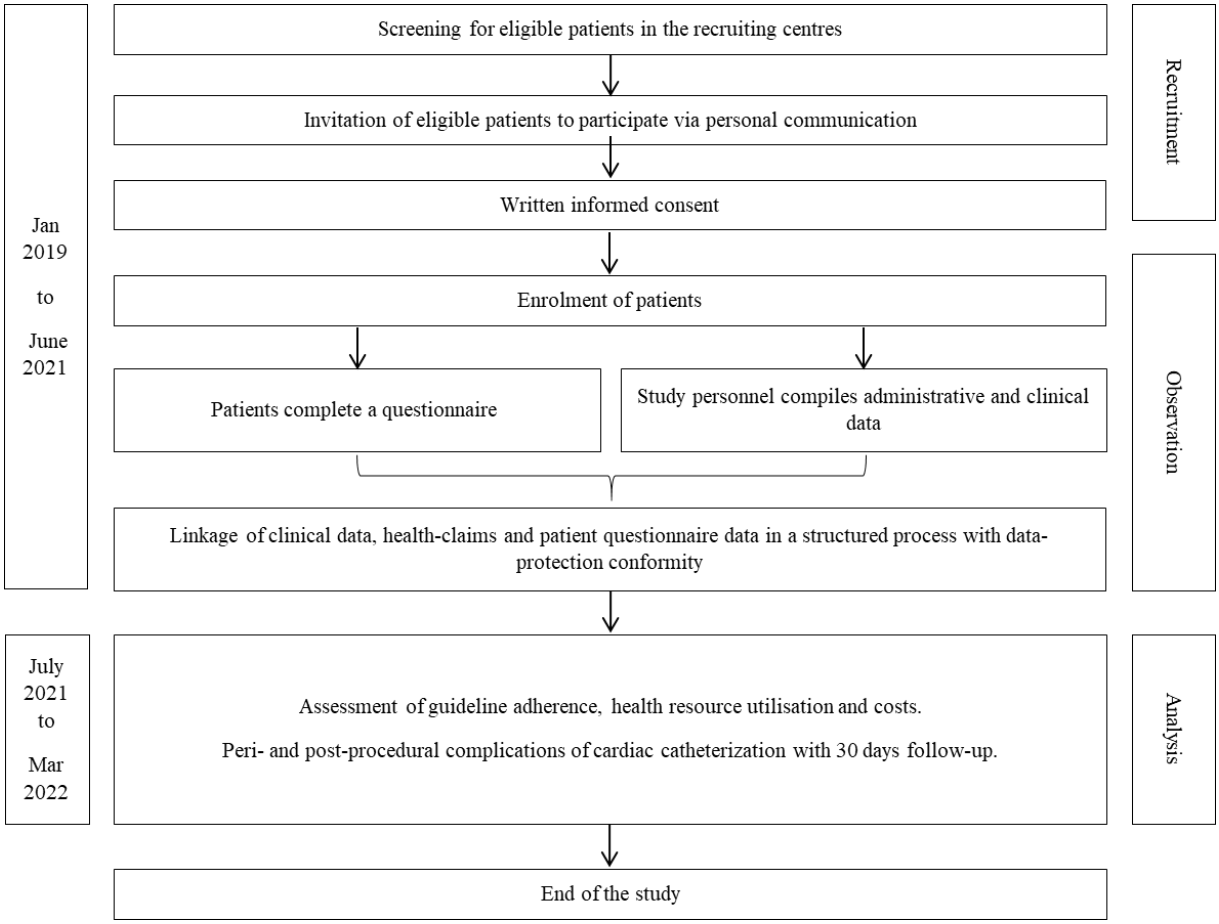

Figure 1: Flow of participants and collection of data

Outcome measures

The *primary outcome measure* is the proportion of guideline-adherent diagnostic pathways for use of CA. Thereby, the guideline adherence to the German National Disease Management Guideline „Chronic CAD" and the Guidelines of the ESC on "Diagnosis and management of chronic coronary syndromes" in selecting patients for CA is assessed[3,5]. For patients presenting

to the emergency department but with exclusion of an acute myocardial infarction, guideline-adherence is additionally assessed using the "2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation"[18].

The central variable to determine the appropriateness of the indication for CA with the preceding diagnostic pathway in patients not presenting to the ED is the patient's pre-test probability (PTP) for having an obstructive SCAD. Using age, gender and the nature of symptoms (typical, atypical, non-anginal chest pain or dyspnoea), the PTP will be determined based on the predictive model of Diamond et al. and Genders et al. with current data of Juarez-Orozco et al.[4,19,20]. The correct classification of the different types of chest pain depends on a correct medical history taking. Typical angina is defined by meeting all three characteristics of having (i) a constricting discomfort in front of the chest or in the neck, jaw, shoulder or arm, which is (ii) precipitated by physical activity and (iii) relieved by rest or nitrates within 5 minutes. Atypical angina is defined by meeting two, non-anginal chest pain by meeting one or none of these characteristics[3]. For the ENLIGHT-KHK trial the nature of symptoms is acquired using a self-designed standardized patient questionnaire in which the description of symptoms (i.e. duration, location and quality of anginal symptoms) is aligned on the clinical classification used in the Guidelines of the ESC on "Diagnosis and management of chronic coronary syndromes"[3] and the corresponding German wording as used in the German National Disease Management Guideline „Chronic CAD"[5].

Because the PTP for having an obstructive SCAD differs between the guidelines, with the PTP of the latest ESC guidelines being much lower than that in the current German National Disease Management Guideline, adherence is evaluated for both separately. Table 1 summarizes the guideline recommendations which are the basis to define guideline-adherence of the diagnostic pathway and CA, respectively.

Table 1: Summary and comparison of guideline recommendations for patients with suspected obstructive stable coronary artery disease or Troponin-negative patients presenting to the emergency department

	German National Disease Management Guideline SCAD[5]	**ESC Guidelines Chronic Coronary Syndrome[3]**	**ESC Guidelines on non-ST elevation myocardial infarction[18]**
No further testing	PTP < 15%	PTP <5%	Not fulfilling criteria for coronary angiography, management according to SCAD guidelines with PTP <5%.
Non-invasive testing with imaging (e.g. Stress-echocardiography or cCTA)	PTP 15-85%	PTP ≥5%	Not fulfilling criteria for coronary angiography, management according to SCAD guidelines with PTP >5%
Invasive Coronary Angiography	PTP >85% Signs of ischemia during non-invasive testing.	No direct referral to coronary angiography without non-invasive testing (highest PTP is 52%). Signs of ischemia during non-invasive testing.	Diabetes mellitus, or Chronic kidney disease, or Preceding myocardial infarction (3 months), or Preceding bypass-surgery or stent-implantation, or Resting left ventricular ejection fraction <40%

SCAD, stable coronary artery disease; PTP, pre-test-probability; cCTA, coronary computed tomography angiography.

The *primary safety outcome measure* is a composite of peri- and post-procedural major adverse cardiovascular events (MACE) (i.e. myocardial infarction, stroke, and all-cause death up to 30 days after CA). In-hospital complications are obtained from the medical record as documented by the treating physicians and health-claims data. Post-discharge the assessment is solely based on the health-claims data provided by the participating SHIs using a predefined validated set of variables which are used as quality indicators in the German health care system[21,22].

S*econdary outcome measures* are:

- Proportion of patients undergoing coronary revascularization by PCI or coronary artery bypass grafting (CABG);
- Proportion of patients experiencing periprocedural complications: All-cause mortality, myocardial infarction, stroke, significant arterial dissection with stent implantation, cardiogenic shock, emergency CABG, and other complications;

- Proportion of patients experiencing following post-procedural complications (up to 30 days after CA): Myocardial infarction, cardiogenic shock, stroke or transient ischemic attack, acute kidney failure/new dialysis requirement, vascular access complications (e.g. embolization), bleeding complications requiring transfusion, death;
- Proportion of patients experiencing guideline-based functional and anatomical non-invasive testing (e.g. stress-echo, cCTA) for establishing a diagnosis of an obstructive SCAD;
- Medical costs (resource use and prices of invasive and non-invasive testing for obstructive SCAD) of the current clinical practice.

Table 2 lists the different outcomes measures and their data sources.

Table 2: Outcome measures and data sources

Outcomes	**Construct**	**Content/Variables**	**Data source**
Primary outcome measure Guideline adherence	Pre-test probability[4,19,20]	-Age and sex -Nature of anginal symptoms and dyspnoea	-Administrative and clinical data -Patient questionnaire (self-designed) data
	Cardiac catheterization	Test modalities and performance	Clinical data
	Functional and anatomical non-invasive testing	Test types and performance	-Administrative and clinical data -Patient questionnaire (self-designed) data
Primary safety measure MACE (i.e. myocardial infarction, stroke, and all-cause death)			-Clinical data (i.e. clinical assessment of the treating physicians) -SHI claims data[21,22]
Secondary outcome measures			
Coronary revascularization by PCI or CABG			-Administrative and clinical data
Peri- and post-procedural complications			-Clinical data (i.e. clinical assessment of the treating physicians) -SHI claims data[21,22]
Guideline-based functional and anatomical non-invasive testing			Administrative and clinical data
Medical costs of the current clinical practice			SHI claims data

MACE, major adverse cardiovascular events; SHI, Statutory health insurance; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting.

Data collection and management

Data collection and management are conducted according to the International Conference on Harmonisation-Good Clinical Practice (ICH-GCP) guidelines[23] and current data protection regulations. Table 3 shows the various data types, sources, and collection methods.

Table 3: Data types, sources and collection methods in ENLIGHT-KHK: i) administrative and clinical data, ii) standardized questionnaire-based survey data, and iii) claims data of the health insurances AOK Rheinland/Hamburg and NORDWEST which are obtained from each participant

Data source	Content/Variables	Data collection
Administrative and clinical data	- Master and admission data (i.e. demographics and reasons for admission) - Patient characteristics (i.e. risk factors and comorbidities) - Clinical anamnesis (i.e. classification and severity of anginal symptoms) - Non-invasive testing (i.e. test types, test dates and results) - Cardiac catherization (i.e. test dates and results) - Pre- and post-procedural laboratory values - Medication on admission and discharge (e.g. antianginal medication) - Peri- and post-procedural complications (until discharge) associated with a cardiac catheterization	Documented by the study personnel in the recruiting hospitals via an eCRF
Self-designed standardized questionnaire	- Nature of symptoms (i.e. duration, location and quality, severity CCS grading) - Exercise level (i.e. dyspnoea) - Previous non-invasive testing performed by general practitioners, cardiac specialists and hospitals (in- and outpatient)	Completed by the patients and transferred to an eCRF
Claims data	- Peri- and post-procedural complications associated with a cardiac catheterization (based on ICD [24]) - Diagnoses (based on ICD) - Invasive and non-invasive testing (based on OPS- and EBM-Classification) - Costs (based on DRG[25] and EBM[26])	Provided by two statutory health insurances

eCRF, electronic case report form; CCS, Canadian Cardiovascular Society; ICD, International Statistical Classification of Diseases 10th Version; OPS, German Procedure Classification ("Operationen- und Prozedurenschlüssel"); EBM, German Uniform Assessment Standard ("Einheitlicher Bewertungsmaßstab"); G-DRG, German Diagnosis-Related Groups.

Administrative and clinical data are collected via an electronic case report form (eCRF) in the recruiting sites and are transferred to the Cardiovascular European Research Center (CERC). The eCRF is based on an a-priori defined data handbook and is provided via a web-based interface. To facilitate data entry and improve reliability, different query tools are used (e.g. tools for previously performed tests depending on the selected subcohort). The standardized questionnaire will be completed by the patients and transmitted to the eCRF by the study personnel. SHI claims data is provided by the AOK Rheinland/Hamburg and AOK

NORDWEST based on a pre-defined data dictionary and is transmitted to the CERC. Finally, administrative and clinical data, the results from the patient questionnaires and claims data are linked to a combined database by CERC and provided to the University Hospital of Cologne for economic analyses. The data transfer between the CERC, the insurers and the University Hospital of Cologne is conducted through encrypted exchange via the software Cryptshare.

Confidentiality will be maintained at all levels of data collection and management. For this purpose, personal information and patient-level data are stored separately by a project data trust which is not involved in the data analysis. The recruiting sites do not store data or have access to the combined database. Insurers are informed about their participating insurees, however, they have no insight into the patient-level data obtained in the hospitals at any point in time. All data the University Hospital of Cologne receives are pseudonymized.

Sample size

This study aims to enrol 1,500 patients (1,300 in the main cohort and 200 in the secondary cohorts). Although no power calculation is prerequisite for the outlined research objectives, the intended sample size is derived on the basis of published data. Assuming a non-adherence rate between 10% and 25% and a periprocedural complication rate of diagnostic cardiac catheterization of 0.8%[27], about 1,500 patients are required to show that between one and three complications can be avoided with optimal guideline adherence.

Statistical analyses

Descriptive information about study population will be provided. It will include various variables, such as patients' demographics, risk factors, comorbidities and symptoms.

Outcome measures will be analysed using descriptive methods. Both the *primary outcome measure* as the guideline-adherent diagnostic pathways for use of CA and the *primary safety measure as* MACE up to 30 days after CA will be analysed as a binary outcome (i.e. guideline-adherent or not and event occurred or not, respectively) and will be presented in absolute and relative frequencies including 95% confidence intervals. For *secondary outcomes*, continuous data (e.g. costs) will be presented as means with standard deviations or, if appropriate, the median with the interquartile range. Binary data (e.g. coronary revascularization by PCI) will be presented in absolute and relative frequencies (including 95% confidence intervals).

Subgroup analyses will be made for various patients' characteristics (e.g. gender, comorbidities) and the nature of symptoms (e.g. chest pain). If required, adjustments will be

made for possible confounding variables by regression analyses. Further, analyses on positive and negative predictive values of non-invasive testing (e.g. stress-echo, cCTA) in clinical practice and on predictors of guideline adherence/non-adherence by the use of logistic regression are planned.

An economic analysis will be conducted from the perspective of the German SHI. Using a decision-analytic model, a cost-effectiveness analysis[28] will be conducted. Based on the differences in costs and clinical outcomes (i.e. MACE) between the observed and an assumed perfect guideline adherence, the cost per avoided complication will be assessed. The robustness of results will be analysed by different sensitivity analyses[29, 30].

SAS® 9.4 (SAS Institute Inc., Cary, North Carolina) and SPSS® 26 for Windows (SPSS Inc.®, Chicago, IL, USA) will be used for descriptive analyses and TreeAge Pro Healthcare 2017© (Williamstown, Massachusetts) for health economic modelling.

Control for a potential selection bias

To control for a potential selection bias three indicators are determined using health claims data of the participating health insurance companies. These indicators are (i) the proportion of the annual volume of percutaneous coronary interventions to all coronary angiographies, (ii) the proportion of the annual volume of coronary angiographies with preceding non-invasive image guided testing to all coronary angiographies, and (iii) the proportion of the annual volume of fractional-flow-reserve or instantaneous wave-free ratio measurements to all coronary angiographies. To detect a selection bias in recruited patients on a centre level, potential differences in the indicators between recruited an all patients are evaluated. The comparison of the indicators during the three years prior to trial initiation and during the recruitment phase will ensure to control for the Hawthorne effect. Last, to compare the pre-existing level of guideline adherence in participating versus non-participating centres, all centres in North Rhine-Westphalia and Hamburg are benchmarked using the above-mentioned indicators.

Assessment of potential barriers and facilitators of guideline non-adherence

Since unknown multifactorial and trans-sectoral aspects (e.g. organizational factors) may influence guideline-adherent decision-making process[31,32], ENLIGHT-KHK aims to identify these aspects via qualitative interviews with clinical experts. For this purpose, general practitioners and cardiologists in in- and outpatient care will be interviewed as field experts of the German health-care-setting (anticipated n=15–20)[33]. Particularly, the gatekeeper-role of

general practitioners in primary care will be emphasized. Clinical experts will be recruited by field-intern researchers. Data will be collected iteratively via telephone interviews and analysed via content-related classification of categories[34].

Discussion

ENLIGHT-KHK aims to evaluate the potential deviations in clinical decision-making from current guidelines and the clinical and economic implications of these deviations in patients with suspected obstructive SCAD in the German health-care setting.

A particular strength of this study is the linkage of primary (i.e. clinical and patient survey-data) and secondary (i.e. claims data) data which gives a multi-faceted picture of the current care and pathways. This approach allows to evaluate the degree and implications of potential guideline non-adherence in the diagnostic process of patients undergoing CA. Furthermore, it will allow to assess the clinical and economic implications of an inappropriate usage of non-invasive, and invasive procedures, especially that of cardiac catheterization. Additionally, qualitative interviews with clinical experts on factors hindering and facilitating guideline non-adherence should provide a profound understanding of the broader scope and the challenges within the decision process for selecting invasive testing.

Based on the results, recommendations to improve guideline adherence and to ensure the appropriate care for patients with suspected obstructive SCAD and the use of non-invasive and invasive testing will be developed. As part of this research project these recommendations will be integrated into incentive-based contract- and reimbursement models. These models should stimulate resource-efficient and guideline-based care for patients with suspected obstructive SCAD in the German healthcare settings.

Some limitations might be inherent to this study design. First, the occurrence of catheter-related complications until discharge are collected from the patients' medical records and are based on the clinical assessment of the treating physicians (i.e. not adjudicated by a clinical evaluation committee) which may result in some variations in criteria decisive for the diagnosis. For example, the diagnosis of myocardial infarction can be based on the electrocardiographic changes or the imaging evidence. However, to enhance the reliability, the occurrence of complications up to 30 days after CA is also collected based on a validated set of variables which are used as quality indicators by the participating SHI funds and will be utilized for verification. Second, to evaluate a potential selection bias at the participating centres, claims data are used to detect potential differences between included and non-included patients.

Furthermore, claims data are used to evaluate deviations in the level of guideline adherence between participating and non-participating centres. Third, accounting for differences in the healthcare settings of rather rural and rather urban areas, centres from both areas are recruited. Lastly, the study involves the supply regions of two SHI funds (i.e. the AOK Rheinland/Hamburg and the AOK NORDWEST). Accordingly, this might be considered as a limitation of the research project since conclusions based on the study's results cannot necessarily be generalised for nationwide clinical practice. However, the deduced incentive-based contract- and reimbursement models can serve as a solid basis for SHI funds which can be adjusted for local requirements. Supplementary research activities such as the ongoing KARDIO-study for evaluating regional variations in utilizing cardiac catheterizations in Germany[35] might additionally tackle this limitation.

In conclusion, ENLIGHT-KHK will provide first insights on the appropriate and guideline-adherent use of CA in patients with suspected obstructive SCAD and, an increased understanding of the clinical and economic consequences of varying diagnostic pathways. The project will be a first step in the evidence-based acquisition and trans-sectoral optimisation of the current clinical practice of patients with suspected obstructive SCAD in the German health-care setting.

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Ethics and dissemination: This study received a leading Ethics Approval (2018/12/13) from the ethics committee of the Ärztekammer Nordrhein (Nr. 2018361). Further ethics approval is sought from all participating sites. The dissemination of results takes place via presentations at conferences and publications in peer-reviewed journals.

Registration details: German Clinical Trials Register DRKS00015638, Registered 19.02.2019**;** Universal Trial Number (UTN): U1111-1227-8055.

Health Condition or Problem studied: ICD10: I20 - Angina pectoris; ICD10: I25 - Chronic ischaemic heart disease; ICD10: R07 - Pain in throat and chest.

Recruitment status: Recruitment ongoing (July 2020: 482).

CRediT authorship contribution statement: Yana Seleznova: Methodology, Investigation, Writing – original draft,Writing - review & editing. BastianWein: Methodology, Conceptualization, Project administration, Supervision, Writing - review & editing, Funding acquisition. Dirk Müller: Conceptualization, Methodology, Supervision, Writing - review & editing, Funding acquisition. Marie Naumann: Methodology, Writing - review & editing. Oliver Bruder: Conceptualization, Supervision. Melanie Steffen: Investigation. Ute Windhövel: Data curation, Funding acquisition. Simon Loeser: Conceptualization, Supervision, Funding acquisition. Jörg Artmann: Conceptualization, Investigation. Thomas Fritz: Funding acquisition. Melanie Eckardt: Investigation. Stephanie Stock: Supervision. Christoph Kurt Naber: Conceptualization, Funding acquisition.

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References

1. Leal J, Luengo-Fernández R, Gray A, Petersen S, Rayner M. Economic burden of cardiovascular diseases in the enlarged European Union. *Eur Heart J* 2006;**27**:1610–1619.

2. OECD. Health at a Glance 2019: OECD Indicators. Paris: OECD Publishing; 2019. https://doi.org/10.1787/4dd50c09-en.

3. Knuuti J, Wijns W, Saraste A, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J* 2020;**41**:407–477.

4. Genders TS, Steyerberg EW, Alkadhi H, et al. A clinical prediction rule for the diagnosis of coronary artery disease: validation, updating, and extension. *Eur Heart J* 2011;**32**:1316–1330.

5. Bundesärztekammer (BÄK), Kassenärztliche Bundesvereinigung (KBV), Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF) 2019. National disease management guidelines for chronic CAD (NVL)—long version, 5th edition. www.khk.versorgungsleitlinien.de https://doi.org/10.6101/AZQ/000419.

6. Figulla H, Lauten A, Maier L, Sechtem U, Silber S, Thiele H. Percutaneous coronary intervention in stable coronary heart disease – is less more? *Dtsch Arztebl Int* 2020;**117**:137–144.

7. Mühlberger V, Kaltenbach L, Ulmer H, Pachinger O. Herzkathetereingriffe in Österreich im Jahr 2013 (mit Audit bis 2014) [Cardiac catheterization in Austria during the year 2013 (Registry Data with Audit including 2014)]. *J Kardiol* 2015;**22**:22–26.

8. Brause M, Grande G, Mannebach H, Badura B. Der Einfluss sozialer und struktureller Faktoren auf die Angemessenheit invasiver kardiologischer Prozeduren [The impact of social and institutional characteristics on the appropriateness of invasive cardiologic procedures]. *Med Klin* (Munich) 2006;**101**:226–234.

9. Institute for Quality Assurance and Transparency in Healthcare (IQTiG) 2016. Bundesauswertung zum Erfassungsjahr 2015 für Koronarangiographie und Perkutane Koronarintervention (PCI): Qualitätsindikatoren, https://iqtig.org/downloads/auswertung/2015/21n3koropci/QSKH_21n3-KORO-PCI_2015_BUAW_V02_2016-07-07.pdf (30 June 2020).

10. Möckel M, Searle J, Jeschke E. *Indikation, Prognose und regionale Unterschiede der Herzkatheterversorgung in Deutschland*. 1 edn. In: Versorgungs-Report 2013/2014. editors. Klauber J, Günster C, Gerste B, Robra BP and Schmacke N. Stuttgart: Schattauer; 2014, p231–254.

11. Desai NR, Bradley SM, Parzynski CS, et al. Appropriate use criteria for coronary revascularization and trends in utilization, patient selection, and appropriateness of percutaneous coronary intervention. *JAMA* 2015;**314**:2045–2053.

12. Puri P, Carroll J, Patterson B. Cost savings associated with implementation of peer-reviewed appropriate use criteria for percutaneous coronary interventions. *Am J Cardiol* 2016;**117**:1289–1293.

13. Federal Joint Committee (GBA) 2019. Richtlinie des Gemeinsamen Bundesausschusses zur datengestützten einrichtungsübergreifenden Qualitätssicherung, https://www.g-ba.de/downloads/62-492-2148/DeQS-RL_2019-11-22_iK-2020-05-16_AT-15-05-2020-B2.pdf (29 June 2020).

14. The Federal Statistics Office (Destatis) 2015. Krankheitskosten in Mio. € für Deutschland. Gliederungsmerkmale: Jahre, Alter, Geschlecht, ICD10, http://www.gbe-bund.de/gbe10/i?i=63:38480687D (30 June 2020).

15. Baldus S, Werdan K, Levenson B, Kuck KH. Klug entscheiden: … in der Kardiologie. *Dtsch Arztebl* 2016;**113**:A-1312/B-1103/C-1085.

16. Benchimol EI, Smeeth L, Guttmann A, et al. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement. *PLoS Med* 2015;**12**:e1001885.

17. Swart E, Gothe H, Geyer S, et al. Gute Praxis Sekundärdatenanalyse (GPS): Leitlinien und Empfehlungen [Good practice of secondary data analysis (GPS): guidelines and recommendations]. *Gesundheitswesen* 2015;**77**:120–126.

18. Roffi M, Patrono C, Collet JP, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2016;**37**:267–315.

19. Diamond GA, Forrester JS. Analysis of probability as an aid in the clinical diagnosis of coronary-artery disease. *N Engl J Med*. 1979;**300**:1350–1358.

20. Juarez-Orozco LE, Saraste A, Capodanno D, et al. Impact of a decreasing pre-test probability on the performance of diagnostic tests for coronary artery disease *Eur Heart J Cardiovasc Imaging* 2019;20:1198–1207.

21. AOK Research Institute (WIdO) 2020. https://wido.de/institut-team/about-wido/ (7 October 2020).

22. AOK Research Institute (WIdO) QSR-Verfahren 2019. Indikatorenhandbuch Verfahrensjahr 2019. https://www.qualitaetssicherung-mit-routinedaten.de/imperia/md/qsr/methoden/indikatorenhandbuch_2019_final.pdf (7 October 2020).

23. ICH harmonised guideline integrated addendum to ICH E6(R1): Guideline for Good Clinical Practice ICH E6(R2) ICH Consensus Guideline. https://ichgcp.net/ 2016 (30 June 2020).

24. German Institute of Medical Documentation and Information (DIMDI) 2019. International Statistical Classification of Diseases and Related Health Problems 10. Revision German Modification (ICD-10-GM). https://www.dimdi.de/static/de/klassifikationen/icd/icd-10-gm/kode-suche/htmlgm2019/ (30 June 2020).

25. Institute for the Hospital Remuneration System (InEK) 2019. German Diagnosis Related Groups Version 2019. https://www.g-drg.de/G-DRG-System_2019 (30 June 2020).

26. The National Association of Statutory Health Insurance Physicians (KBV) 2019. German Uniform Assessment Standard (EBM), https://www.kbv.de/html/arztgruppen_ebm.php#content2398 (30 June 2020).

27. Ammann P, Brunner-La Rocca HP, Angehrn W, Roelli H, Sagmeister M, Rickli H. Procedural complications following diagnostic coronary angiography are related to the operator's experience and the catheter size. *Cathet Cardiovasc Intervent* 2003;**59**:13–18.

28. Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. *Methods for the economic evaluation of health care programmes*. 4th ed. Oxford: Oxford University Press; 2015.

29. Briggs AH, Weinstein MC, Fenwick EA, Karnon J, Sculpher MJ, Paltiel AD: Model parameter estimation and uncertainty analysis: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force Working Group-6. *Med Decis Making*. 2012;**32**:722–732.

30. Briggs A, Claxton K, Sculpher M. *Decision modelling for health economic evaluation*. Reprinted ed. Oxford: Oxford University Press; 2011.

31. Cabana MD, Rand CS, Powe NR, et al. Why don't physicians follow clinical practice guidelines? A framework for improvement. *JAMA* 1999;**282**:1458–1465.

32. Hoorn C, Crijns H, Dierick-van Daele ATM, Dekker LRC. Review on factors influencing physician guideline adherence in cardiology. *Cardiol Rev* 2019;**27**:80–86.

33. Meuser M, Nagel U. The expert interview and changes in knowledge production. In: Bogner A, Littig B, Menz W, editors. *Interviewing Experts*. London: Palgrave Macmillan; 2009, p17–42.

34. Mayring P. *Qualitative content analysis: theoretical foundation, basic procedures and software solution.* Klagenfurt: Beltz; 2014.

35. KARDIO study. Trial description. German Clinical Trials Register (DRKS) 2020. https://www.drks.de/drks_web/navigate.do?navigationId=trial.HTML&TRIAL_ID=DRKS00021165 (20 June 2020).

Chapter 7 Dissertation project III: Economic evaluation

Health economic consequences of optimal vs. observed guideline adherence of coronary angiography in patients with suspected obstructive stable coronary artery in Germany: a microsimulation model.

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Abstract

Aims: While the number of patients with stable coronary artery disease (SCAD) is similar across European countries, Germany has the highest per capita volume of coronary angiographies (CA). This study evaluated the health economic consequences of guideline-non-adherent use of CA in patients with SCAD.

Methods and results: As part of the ENLIGHT-KHK trial, a prospective observational study, this microsimulation model compared the number of major adverse cardiac events (MACE) and the costs of real-world use of CA with those of (assumed) complete guideline-adherent use (according to the German National Disease Management Guideline 2019). The model considered non-invasive testing, CA, revascularization, MACE (30 days after CA), and medical costs. Model inputs were obtained from the ENLIGHT KHK trial (i.e. patients' records, a patient questionnaire, and claims data). Incremental cost-effectiveness ratios were calculated by comparing the differences in costs and MACE avoided from the perspective of the Statutory Health Insurance (SHI). Independent on pre-test probability (PTP) of SCAD, complete guideline adherence for usage of CA would result in a slightly lower rate of MACE (–0.0017) and less cost (€–807) per person compared with real-world guideline adherence. While cost savings were shown for moderate and low PTP (€901 and €502, respectively), for a high PTP, a guideline-adherent process results in slightly higher costs (€78) compared with real-world guideline adherence. Sensitivity analyses confirmed the results.

Conclusion: Our analysis indicates that improving guideline adherence in clinical practice by reducing the amount of CAs in patients with SCAD would lead to cost savings for the German SHI.

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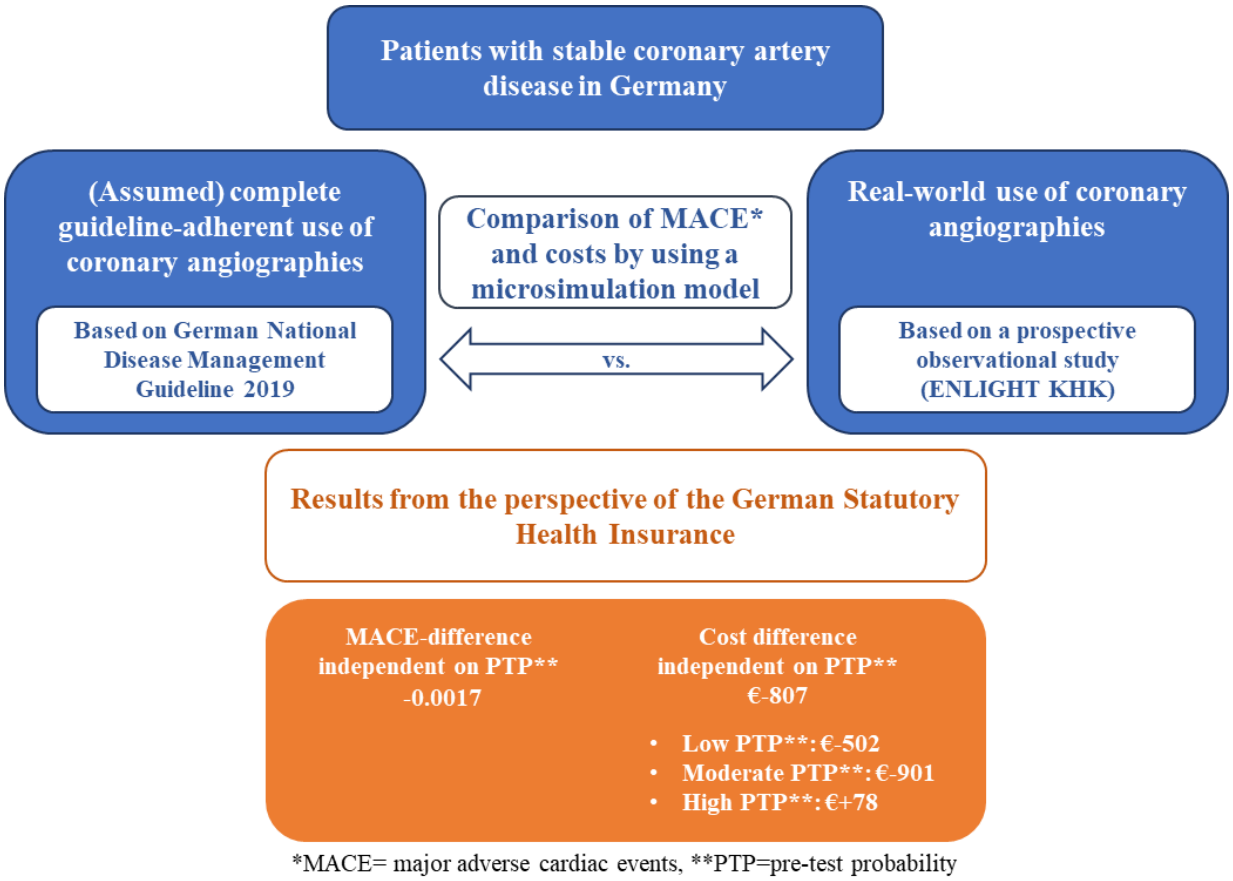
Graphical Abstract

Analysis of health economic consequences of optimal vs. observed guideline adherence of coronary angiography in patients with suspected obstructive stable coronary artery in Germany.



*MACE= major adverse cardiac events, **PTP=pre-test probability

Keywords Coronary angiography, Guideline adherence, Chronic coronary artery disease, Economic Evaluation, Costs

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Introduction

The diagnostic work-up of suspected stable coronary artery disease (SCAD) can be challenging because up to 85% of potentially attributable symptoms, especially chest pain, are not caused by myocardial ischemia/obstructive CAD.[1] Decision support in clinical practice is provided by clinical guidelines for the management of SCAD, such as the German National Disease Management Guideline 2019 (GNDMG), which is adopted from the 2013 ESC guidelines on the management of SCAD.[2] Based on pre-test probability (PTP), these recommend an algorithmic use of five non-invasive testing (NIT) options in patients with an intermediate PTP (15–85%) (i.e. coronary computed tomography angiography (cCTA), stressechocardiography (stress-echo), stress cardiac magnetic resonance imaging (stress-CMR), myocardial perfusion scintigraphy (MPS), exercise electrocardiogram (eECG)), or a direct coronary angiography (CA) in patients with a PTP > 85%.[3]

In 2019, 1053 CAs per 100 000 citizens were performed in Germany.[4] At similar base-line risk, ~690 per 100 000 Cas were performed in Austria and 600 per 100 000 in Switzerland.[5] For Switzerland, a substantial overuse of inappropriate CAs was concluded.[6] Additionally, for Germany almost 1.5 times more percutaneous coronary interventions (PCI) were reported than for Austria (433 vs. 300 per 100 000),[4,5] which corresponds to the highest number of PCIs across OECD countries.[7] In addition, documented regional differences in the use of PCIs and CAs[8,9] have raised the question whether these findings truly reflect differences in medical needs in Germany.[8–10] However, recent evidence[11] indicated an association of supply factors with utilization. This evidence may indicate a substantial degree of non-adherence to clinical guidelines in Germany.[7,8,12]

Although there is a long-standing debate on the number of CAs in Germany,[7,8,11,13] evidence on guideline adherence in the use of CA in patients with suspected obstructive SCAD in Germany was lacking.[14] Therefore, the ENLIGHT-KHK trial was registered in February 2019 to examine prospectively the extent of guideline adherence of CA-use and the resulting health economic consequences in Germany.[15]

To estimate the clinical and monetary consequences resulting from the current use of CA in everyday clinical practice (hereafter ‘realworld CA-use’), we compared the related number of avoided major adverse cardiovascular events (MACE) and costs with those of an assumed

complete guideline-adherent use of CA (hereafter 'adherent CA-use'). The incremental costs and effectiveness were determined from the third-party payer perspective, the German Statutory Health Insurance (SHI).

Methods

Our analysis was based on the ENLIGHT-KHK trial, a multicentre, prospective observational study which recruited 901 patients with suspected SCAD who presented to one of nine hospitals (2019–2021) in Germany.[15] Because the harming potential of CA is considered to be low,[16] a cost-minimization analysis (i.e. analysing only costs while assuming same effects) would have been an obvious option. However, because the underlying ENLIGHT-KHK trial was not designed as a non-inferiority trial—which is a precondition of cost-minimization analyses[17]–we conducted a full cost-effectiveness analysis.[15] The analysis was reported according to the Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022)[18] (see checklist in the Supplementary material, Table S1).

An incremental cost-effectiveness ratio (ICER) was calculated by dividing the differences in costs and avoided MACE (e.g. as done in the BASKET trial[19,20]) between 'adherent CA-use' and 'real-world CA-use'.[21] With respect to the study perspective (i.e. the German SHI), only direct medical costs were included.[22,23] Because both clinical and monetary consequences resulting from CA beyond a period of 1 year are unlikely,[24] for the analysis, a 1-year time horizon was applied.

Patient population and comparators

Patient data were obtained from the ENLIGHT-KHK trial, considering different PTP of SCAD. Among all 901 patients, 34 (3.8%) had a low PTP (<15%), 773 (85.8%) a moderate (15–85%), and 48 (5.3%) a high PTP (>85%) of SCAD. Patients were at mean 64.9 (SD 11.8) years old, and 524 (58.2%) of them were male. Supplementary material, Table S2, gives an overview of patients' characteristics.

Patients in the model underwent a decision-making process for receiving a CA in order to confirm or exclude an obstructive SCAD either based on (i) 'adherent CA-use' (i.e. assumed guideline adherence of 100% for receiving CA) or (ii) 'real-world CA'. 'Adherent CA-use' was simulated based on recommendations for using CA according to the GNDMG,[3] while 'real-

world CA-use' was estimated based on the observed use of CA in ENLIGHT-KHK (i.e. reflecting guideline adherence in current clinical practice).

Model description

We developed a microsimulation model[25] to capture the costs and MACE of the 'real-world CA-use' and the 'adherent CA-use'. Patients with suspected obstructive SCAD underwent a process outlined in Figure 1 (either based on 'adherent CA-use' or on 'real-world CA'). Patients with clinical suspicion for SCAD, in which CAD could not be ruled out a priori, received initial diagnostic management (including e.g. an electrocardiogram or an echocardiography at rest). Based on this first assessment, patients were then assigned either to a first-line CA (i.e. direct CA without prior NIT) or they received a NIT: (i) cCTA, (ii) stress-echo, (iii) stress-CMR, (iv) MPS, or (v) eECG. In patients with a negative NIT-result, a SCAD was ruled out, while in those with a positive or an inconclusive NIT result, patients could receive a CA. Patients with a CA (first-line or following NIT) who have abnormal results (i.e. one- to three-vessel disease and coronary sclerosis without >50% stenosis) could be revascularized. Revascularization was performed either via percutaneous coronary intervention (PCI) or via coronary artery bypass grafting (CABG). The model was performed with TreeAge Pro 2019© (Williamstown, MA).

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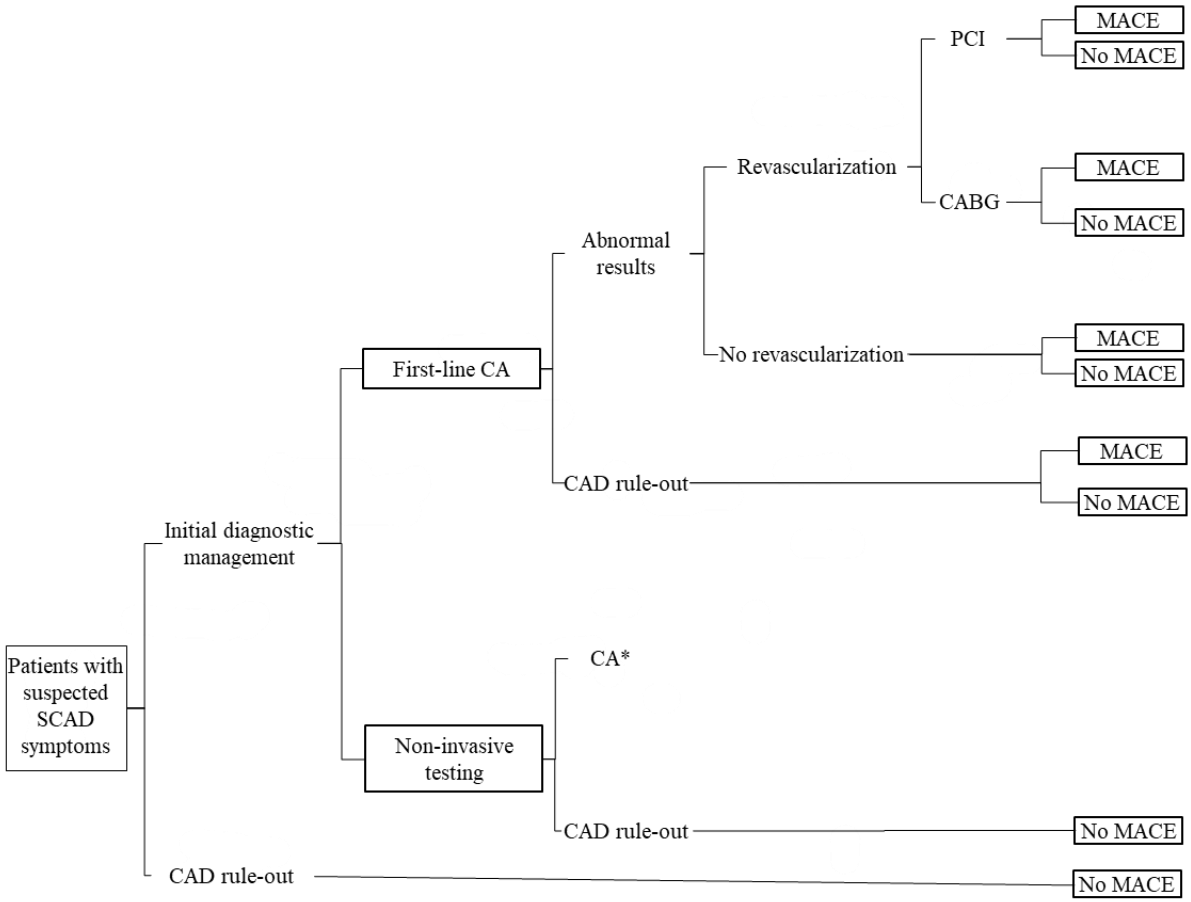

Figure 1: Model overview representing the decision-making process in the diagnostic work-up of patients with suspected SCAD. In the microsimulation model the 'real-world coronary angiography use' is compared with an 'adherent coronary angiography use'. *same structure as the 'first-line CA' pathway.

CA, coronary angiography; CABG, coronary artery bypass graft; CAD, coronary artery disease; SCAD, stable coronary artery disease; MACE, major adverse cardiovascular events.

Model inputs

Data on clinical parameters and costs was obtained from (i) a priori defined evaluating rules according to the GNDMG,[3] (ii) patients' records, (iii) a standardized questionnaire-based survey, and (iv) claims data of the health insurances AOK Rheinland/Hamburg and NORDWEST, which are obtained from each participant.[15]

Guideline adherence

Guideline adherence of CA-use in clinical practice was the primary outcome measure in the ENLIGHT-KHK trial.[15] It was determined according to the GNDMG,3 which is adopted from the 2013 ESC guidelines on the management of SCAD[2] (without being updated for the 2019 ESC guidelines[26]). Guideline adherence was evaluated by using a priori defined evaluating rules

based on data from patients' records and patients' questionnaire. These data included the patient's PTP[1,27] for having an obstructive SCAD and the results of the prior NIT (see Supplementary material, Table S3 for rationale for evaluating guideline adherence). As a result, in all patients undergoing CA, the observed guideline adherence was 25.6% (n = 169), i.e. 24 patients (5.7%) with first-line CA, and 145 patients (61.2%) with prior NIT were treated guideline-adherent (see Table 1).

Table 1: Degree of observed guideline adherence in the clinical practice in the ENLIGHT-KHK trial

Clinical practice (observed)	**Rate (%)**
Overall guideline adherence (n = 659)	169 (25.6)
First-line CA (n = 422)	24 (5.7)
Low PTP (<15%)	0/10 (0)
Moderate PTP (15-85%)	0/388 (0)
High PTP (>85%)	24/24 (1)
CA with prior NIT (n = 237)	145 (61.2)
Low PTP (<15%)	3/4 (0.75)
Moderate PTP (15-85%)	121/212 (0.57)
High PTP (>85%)	21/21 (1)

CA, coronary angiography; NIT, non-invasive testing; PTP, pre-test probability.

Clinical data

To reflect the clinical pathway of patients with suspected obstructive SCAD, data were collected from patient' records.[15] For the model, conditional probabilities were calculated from rates of occurrence.[28]

Because the observed guideline adherence was 25.6%, the 'adherent CA-use' would reduce CAs overall by 74%. To calculate the parameters for 'adherent CA-use' the observed rates of CAs (first-line and with prior NIT) were multiplied with the degree of guideline adherence and then converted to probabilities. As a result, in the 'adherent CA-use' arm, the reductions of CAs lead to an increase of NIT. Other variables were assumed not to differ between the alternatives.

Because the appropriate diagnostic strategy depends on the PTP,[1,29] different probabilities for first-line CA and CA with prior NIT were considered in the model. For example, while in the ENLIGHT-KHK trial, 24 patients with a high PTP (5.7%), ten patients (2.4%) with a low PTP, and 388 (91.9%) with a moderate PTP underwent a first-line CA, in the 'adherent CA-use', only those with a high PTP 24 (5.7%) were recommended to receive a first-line CA (in line with GNDMG[3]). Table 2 lists the clinical input data.

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Table 2: Clinical input data on clinical pathways and MACE for both 'real-world CA-use' and 'adherent CA-use' included in the model

Clinical pathways	Estimate[a] (95% CI)	Source
'Real-world CA-use' (26% observed guideline adherence)		
Initial diagnostic management	0.623 [0.619, 0.627]	Patients' records from nine participating hospitals
First-line CA[b]		
ppt <15% (0.024)	0.292 [0.158, 0.404]	
ppt 15-85% (0.919)	0.401 [0.380, 0.422]	
ppt >85% (0.057)	0.393 [0.301, 0.473]	
SCAD Rule-out after first-line CA	0.234 [0.202, 0.265]	
Revascularization after abnormal first-line CA	0.396 [0.362, 0.428]	
PCI by first-line CA	0.599 [0.581, 0.616]	
CA with prior NIT		
ppt <15% (0.02)	0.231 [0.063, 0.369]	
ppt 15-85% (0.896)	0.457 [0.429, 0.484]	
ppt >85% (0.084)	0.583 [0.524, 0.635]	
Rule-out of SCAD after CA with prior NIT	0.193 [0.151, 0.232]	
Revascularization after abnormal CA with prior NIT	0.420 [0.379, 0.458]	
PCI with prior NIT	0.593 [0.570, 0.616]	
CA-associated MACE[c]		
Diagnostic CA	0.007 [0.001, 0.013]	Patients' records from nine participating hospitals and claims data from AOK Rheinland/Hamburg and AOK NORDWEST
Therapeutic CA (PCI, CABG)	0.011 [0.003, 0.019]	
'Adherent CA-use' (100% guideline adherence)		
First-line CA		Patients' records from nine participating hospitals
ppt <15% (0)	0	
ppt 15-85% (0)	0	
ppt >85% (1)	0.393 [0.301, 0.473]	
CA with prior NIT		
ppt <15% (0.013)	0.179 [0.018, 0.313]	
ppt 15-85% (0.511)	0.295 [0.259, 0.328]	
ppt >85% (0.089)	0.583 [0.524, 0.635]	

CA, coronary angiography; CI, confidence interval; CABG, coronary artery bypass grafting; NIT, non-invasive testing; SCAD, stable coronary artery disease; PCI, percutaneous coronary intervention; PTP, pre-test probability.
[a]For details on clinical data see Supplementary material, Table S4.
[b]First-Line CA means CA without preceding NIT.
[c]For a detailed breakdown of MACE, please see Supplementary material, Text S5.

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The probabilities of catheter-associated MACE included all-cause death, myocardial infarction, and stroke for a period of 30 days after CA (see Table 2). Data on in-hospital MACE were obtained from patients' records (documented by the treating physicians). Post-discharge MACE were based on claims data provided by the two participating SHIs[15] (see Supplementary material, Text S5 for a detailed breakdown of MACE).

In the case of missing values, an imputation was not performed because the highest value did not exceed 5% (see Supplementary material, Table S4).

Resource utilization and costs

According to the perspective of the German SHI,[22,23] we included costs due to (i) diagnostic CA, (ii) NIT, (iii) revascularization, and (iv) treatment of CA-associated MACE (Figure 1). Parameters on resource use and costs were based on claims data from two German insurances (AOK Rheinland/Hamburg and AOK NORDWEST) and patients' records.[15] We estimated average costs per procedure and event, respectively.

Costs of diagnostic CA (€2431) considered CAs without subsequent revascularization and were estimated with regard to the proportion of CAs with fractional flow reserve (FFR). We differentiated between in- and outpatient procedures by valuing the costs according to the German reimbursement rules (i.e. DRG,[30] EBM,[31] and GOP[32]).

Costs of NIT were estimated as weighted average costs according to the resource use of each NIT (i.e. eECG = 35.9%, stress-CMR = 27.2%, cCTA = 20.4%, MPS = 12.8%, and stress-echo = 3.7%). For valuing costs, German unit prices were applied. In the 'adherent CA-use' arm the increased number of NIT (as a result of lesser CAs) was accounted for. Further, in line with the GNDMG,[3] only non-invasive image-guided testing, i.e. cCTA, stress-CMR, stress-echo, or MPS (NIT w/o eECG) was assumed to be included in the 'adherent CA-use'. Costs of outpatient NIT were valued according to the corresponding German reimbursement rules (i.e. EBM[31] and GOP[32]). In the case of CA and subsequent revascularization, the costs of inpatient NIT were assumed to be covered by the assigned DRG for the inpatient treatment.

In the case of revascularization, the costs of CABG or PCI were considered.

To estimate the costs of CA-associated MACE (€6429), the costs of treatment for myocardial infarction (e.g. PCI) and stroke were considered according to the incidence of these events

[reflected by diagnosis codes for myocardial infarction (I21) and stroke (I63)]. Because these treatments were all performed in an inpatient setting, we valued these costs based on DRGs.[30]

Costs were based on data from 2019 to 2021 and provided in 2022 euros. In line with national guidance,[23] we adjusted costs for inflation[21] with respect to the German harmonised index of consumer prices[33] for both inpatient care (e.g. CABG) and outpatient care services (e.g. outpatient CA). Because costs and effects relate to a period of 1 year, they were not discounted.[23] In the case of missing values, we imputed these by using the mean (corrected for outliers) of the corresponding reimbursement rules (e.g. DRG, EBM). Table 3 presents the parameters on resource utilization and costs.

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Table 3: Resource utilization and costs for both 'real-world CA-use' and 'adherent CA-use' included in the model

Cost category	Estimate	Source
Resource utilization	**Proportion (95% CI)**	
'Real-world CA-use' (26% observed guideline adherence)		
CA inpatient[a]	0.765 [0.723, 0.807]	Claims data from the AOK Rheinland/Hamburg and AOK NORDWEST Patients' records from nine participating hospitals
CA outpatient[a]	0.235 [0.193, 0.277]	
CA with FFR[b]	0.079 [0.059, 0.099]	
CA without FFR[b]	0.921 [0.901, 0.941]	
NIT [b]		
cCTA	0.204 [0.169, 0.239]	
Stress-echo	0.037 [0.021, 0.053]	
Stress-CMR	0.272 [0.233, 0.310]	
MPS	0.128 [0.099, 0.157]	
eECG	0.359 [0.318, 0.401]	
'Adherent CA-use' (100% guideline adherence)		
Non-invasive image-guided testing[b]		
cCTA	0.4 [0.358, 0.442]	
Stress-echo	0.05 [0.031, 0.069]	
Stress-CMR	0.40 [0.358, 0.442]	
MPS	0.15 [0.119, 0.181]	
eECG	0.0	
Costs (both comparators)	**Mean in € (95% CI)**	
Diagnostic CA[a]	2431 [2325, 2558]	Claims data from AOK Rheinland/Hamburg and AOK NORDWEST
CA with FFR[c]	3471 [3100, 3823]	
CA without FFR[d]	2342 [2222, 2459]	
cCTA[e]	622 [375, 894]	
Stress-echo[f]	142 [124, 169]	
Stress-CMR[g]	653 [548, 766]	
MPS[h]	444 [332, 590]	
eECG[i]	37 [34, 40]	
PCI[j]	4128 [3992, 4256]	
CABG[k]	18506 [17233, 20174]	
MACE	6569 [5115, 7745]	

CA, coronary angiography; CI, confidence interval; CABG, coronary artery bypass grafting; cCTA, coronary computed tomography angiography; CMR, cardiac magnetic resonance; MACE, major adverse cardiovascular event; MPS, myocardial perfusion scintigraphy; NIT, non-invasive testing; PCI, percutaneous coronary intervention; eECG, exercise electrocardiogram; FFR, fractional flow reserve.

[a] n = 387, [b] Supplementary material Table S4, [c] n = 34, [d] n = 353, [e] n = 38, [f] n = 202, [g] n = 140, [h] n = 63, [i] n = 55, [j] n = 251, [k] n = 26

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Sensitivity analyses

To identify the parameters with the largest impact on the results, we ran univariate deterministic sensitivity analyses for all input parameters.[28] Confidence intervals (95%) were used for the variation of clinical data, resource utilization, and costs (Tables 2–3). In addition, a probabilistic sensitivity analysis using a Monte Carlo simulation with 10 000 iterations was performed to model a simultaneous change of all model parameters except the proportions of inpatient and outpatient CA (Tables 2–3). We defined beta distributions for probabilities and proportions of resource use, and gamma distributions for costs.[28] In addition, to examine an only improved use of CA (i.e. 70–90%) and the impact of real-world CA-use according to the current 2019 ESC Guidelines,[26] several sensitivity analyses were performed (see Supplementary material, Tables S6-S7 for details).

Model validation

To ensure that our model (e.g. structure, inputs) corresponds to current clinical practice, published evidence, and conditions of the decision setting (e.g. perspective and corresponding costs), we iteratively consulted clinical experts and experts from the SHI (face-validity). Further, we compared model inputs obtained from the trial or the SHI (e.g. costs of CA) and model outcomes (i.e. costs of the 'real-world CA-use') with publicly available sources (external validity). Additionally, we compared the model structure and model inputs to those of evaluations examining similar questions[34,35] (cross-validation) (see Supplementary material, Questionnaire S8, for validation efforts[36]).

Results

Base-case analysis

Overall, 'adherent CA-use' reduced the costs of care by €807 per procedure and was associated with a marginal reduction of MACE (–0.0017) compared with 'real-world CA-use'. Limited to patients with low or moderate PTPs, 'adherent CA-use' reduced the costs by €502 and €901, respectively, while for those with a high PTP, 'adherent CA-use' was slightly more expensive than 'real-world CA-use' (plus €78, see Table 4 for detailed results).

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Table 4: Results from the base-case cost-effectiveness analysis of guideline adherence by use of CA in patients with suspected SCAD in Germany

	Costs (€) per person and process	**Cost difference (€) per person and process**	**MACE per person and process**	**Effect difference (averted MACE per person)**	**ICER (€ per averted MACE)**
Overall population					
'Adherent CA-use' (assumed)	1398	-807	0.0019	-0.0017	dominates[a]
'Real-world CA-use' (observed)	2206		0.0036		
PTP <15%					
'Adherent CA-use' (assumed)	388	-502	0	0	undefined
'Real-world CA-use' (observed)	890		0		
PTP 15%-85%					
'Adherent CA-use' (assumed)	1295	-901	0.0017	-0.0018	dominates[a]
'Real-world CA-use' (observed)	2196		0.0035		
PTP >85%					
'Adherent CA-use' (assumed)	2534	78	0.0044	0	undefined
'Real-world CA-use' (observed)	2456		0.0044		

ICER, incremental cost-effectiveness ratio; MACE, major adverse cardiovascular event; PTP, pre-test probability.
[a] 'Adherent CA-use' is less costly and more effective in averting MACE compared with 'real-world CA-use'.

Sensitivity analyses

The results of the deterministic sensitivity analysis are shown in Figure 2. Among different variables assessed, the probability of a CA with prior NIT for patients with moderate PTP in 'adherent CA-use' has the largest influence (+12/–11%) on the incremental costs, followed by the corresponding probability (–6/+5%) in 'real-world CA-use'. The costs of cCTA and CABG had the highest impact on incremental costs (4–5%). The results responded least (≤1%) to changes in the remaining values, including probabilities of CA (first-line and after prior NIT) for patients with low PTP in both arms, the probability of a high PTP in the 'real-world CA-use', and the probabilities for MACE and the associated treatment costs.

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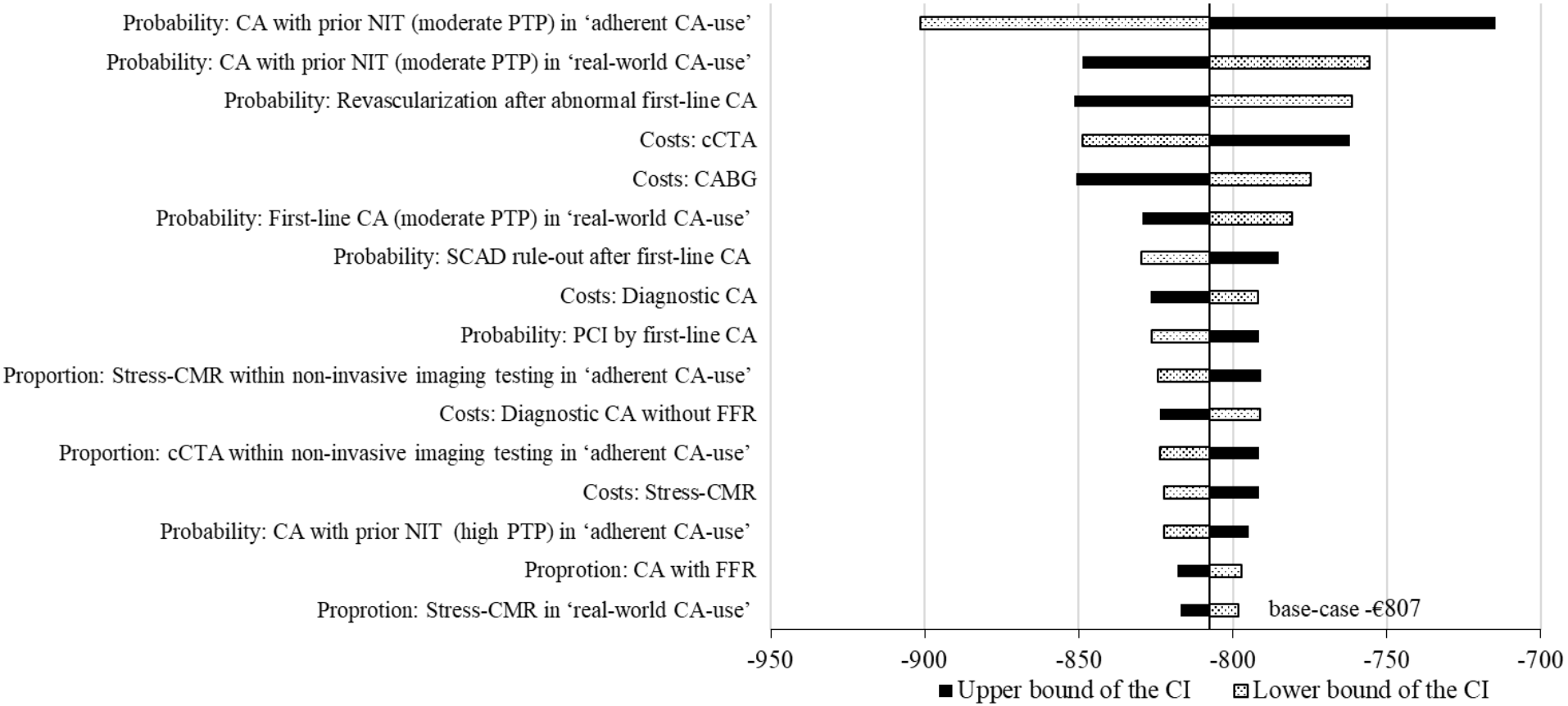

Figure 2: Tornado-diagram presenting the results of the univariate deterministic sensitivity analysis (i.e. parameters with the greatest impact on incremental costs).

CA, coronary angiography; CABG, coronary artery bypass grafting; cCTA, coronary computed tomography angiography; CI, confidence interval; CMR, cardiac magnetic resonance; FFR, fractional flow reserve; NIT, non-invasive testing; PCI, percutaneous coronary intervention; PTP, pre-test probability; SCAD, stable coronary artery disease.

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In the probabilistic sensitivity analysis, 'adherent CA-use' dominates the 'real-world CA-use' in 99% of the iterations (Supplementary material, Figure S9).

By increasing the guideline adherence to 70, 80, or 90%, the costs would be reduced on average by €440, €555, or €669, respectively, compared to 'real-world CA-use' (26%). The difference in MACE would be the lowest (0.0011) for 70% guideline adherence (Supplementary material, Table S10).

By examining the guideline adherence according to the 2019 ESC[26] for the overall population, the costs would reduce by €866 (compared to 'real-world CA-use' (21.3%)). For the different PTP-groups (low, moderate, and high), the costs would decrease by €497, €901, and €837, respectively (Supplementary material, Table S11).

Model validation

The external validation showed that ENLIGHT-KHK data were comparable to data available from public sources. In terms of effectiveness, the marginal incremental effect between 'adherent CA-use' and 'real-world CA-use' (–0.0017) confirms the ex-ante assumptions of CA as a safe and well-established procedure.[16,24] Similarly, the estimated total costs of the 'real-world CA-use' (€2206) were considered to be realistic because these were similar to the reimbursed costs of CA in Germany (F49G, €2534[37]).

Discussion

This is the first analysis which examined the economic consequences of guideline adherence in patients with presumed obstructive SCAD who presented for potential admission for CA in Germany. It showed that 'adherent CA-use' is less expensive and associated with a slightly lower MACE compared with 'real-world CA-use'. The marginal clinical difference (–0.0017) would correspond to a number of 588 patients to be managed guideline-adherent to avoid one MACE. Our findings are in line with the clinical literature, disclosing CA is an established and safe method in cardiology.[16,24]

With regard to costs, the model estimated an overall cost difference of €807 between 'adherent CA-use' and 'real-world CA-use'. This difference approximately corresponds to half of the reimbursement for an outpatient CA (about €400[31]), one-third of an inpatient CA (€2534[37]), or

is even higher than the costs for any NIT w/o eECG (e.g. cCTA[32]). Based on the current number of 600 000 CAs annually in German SCAD-patients,[7] treating at least 10 or 20% of non-adherently managed patients (ca. 444 000) in line with the guideline would result in annual cost savings from €35.8 or €71.7 million for the SHI.

The incremental costs between 'adherent CA-use' and 'real-world CA-use' depend on the PTP of SCAD in the target population. For the majority of patients, i.e. those with a moderate PTP (15–85%), a CA is only recommended for those with a positive[3] or at least inconclusive result of a NIT w/o eECG. Because many patients did not receive a NIT w/o eECG in this subgroup, 'adherent CA-use' had the most cost saving potential in patients with a moderate PTP (€901). For patients with a low PTP (<15%), the cost savings are lower than for the moderate PTP (€502). For this subgroup, the GNDMG recommends neither NIT nor CA but suggests investigating other potential causes (e.g. gastrointestinal or pulmonary) of symptoms.[3] Since in the 'adherent CA-use' arm the guideline adherence of NIT w/o eECG was not assessed, costs of NIT w/o eECG were accumulated, which may have led to an underestimation of the cost saving potential in this PTP-group.

In contrast to patients with a moderate or low PTP, for those with a high PTP (>85%), 'adherent CA-use' would result in slightly higher costs than 'real-world CA-use' (€2534 vs. €2456). According to GNDMG, patients with a high PTP should directly undergo a CA without a prior NIT w/o eECG.[3] Since in 'adherent CA-use' it was not considered whether the NIT w/o eECG were performed in line with the GNDMG,[3] the costs of these tests were also accumulated, and this slightly favoured the 'real-world CA-use' arm.

Since the proportions of different NIT w/o eECG options and their costs are based on German hospital data, which participated in the ENLIGHT-KHK trial, this should be considered when generalizing the results. However, the deterministic sensitivity analysis showed that varying the amount and costs of NIT w/o eECG has only a small impact on incremental costs.

To ensure a guideline-adherent diagnostic work-up in patients with presumed obstructive SCAD in Germany, an increase of NIT w/o eECG is essential. Although there is a lack of data on capacity of NIT w/o eECG in Germany[4] and the number of additionally required tests cannot be estimated yet, the current reimbursement rules indicate a rather low capacity (especially when compared with CA laboratories). For example, the outpatient cCTA and stress-CMR (which are favoured by the GNDMG) are not reimbursed by the SHI and stress-echo is

reimbursed separately since 2020. These reimbursement rules may have impeded a sufficient capacity building of NIT w/o eECG in Germany. As long as constraints with regard to capacities or reimbursement of NIT w/o eECG are existing,[13] improving guideline adherence may remain challenging in Germany.

Further, it should be considered which degree of guideline adherence is appropriate and realistic to be achieved by improved guideline adherence. Although the outcome guideline adherence was evaluated as a binary measure (i.e. adherent or non-adherent classification),[15] it represents a complex construct.[3] This included varying populations as well as NIT and their results, which determined whether a CA was performed in line with the GNDMG.

Moreover, guideline adherence is influenced by various hindering or facilitating factors. Independent on disease area, several reviews[38–40] showed that facilitators and/or barriers refer to (i) different contexts, such as the political and social (e.g. opinion of colleges), (ii) the health organizational system (e.g. resources and equipment), (iii) guideline-related factors (e.g. applicability), (iv) guideline users (e.g. attitudes and behaviour), and (v) the patient (e.g. his or her preferences).[40] A review in cardiology identified factors related to patients, physicians, or organization, particularly a large proportion of female and elderly patients, physicians without cardiologic specialization as providers, and a setting of primary care centres.[41] Factors potentially hindering the guideline adherence for CA-use in stable CAD-patients in Germany, include e.g. patients' preferences for specific diagnostic procedures,[42] or the local capacity for NIT. In addition, hindering or facilitating factors can be reinforced by interactions between each other. For example, in our study, the insufficient local capacity for NIT w/o eECG might result in prolonged waiting times for NIT w/o eECG, which might foster the utilization of CA as a diagnostic tool only. Similarly, even if the local capacity for NIT w/o eECG is sufficient, patients' preference for CA over a NIT w/o eECG (e.g. due to a persuasion of diagnostic certainty) might also foster the immediate use of CA.

The ENLIGHT-KHK study sample was recruited in nine non-university hospitals providing elective CA capacities as well as 24/7 services for patients with acute myocardial infarctions. In Germany, CAs are conducted by 1078 health care providers in general, and 770 non-university hospitals in specific, with a median annual volume of 1000–1499 CA per health care provider.[4,12] With 830–4500 (in median 1330) CA per year, the participating study centres reflected a representative spectrum of health care providers. From a patients' side, with a mean age of 64.9 years and a body mass index of 29.5 kg/m², the ENLIGHTK-KHK population seems

comparable to the German national quality assurance cohort (68.5 years, 28.2 kg/m²) (although the rate of women who underwent CA was higher in the study, i.e. 41.8% vs. 36.1%).[12]

Limitations

Our findings need to be interpreted with caution with respect to some limitations. First, the observed degree of guideline adherence in clinical practice (26%) was based on an observational and noncomparative study design (i.e. the ENLIGHT-KHK trial). Hence, we cannot exclude shortcomings inherent to non-comparative effectiveness research (e.g. risk of selection bias). However, the multicentre, prospective ENLIGHT-KHK trial allowed the linkage of primary (i.e. clinical and patient survey-data) and secondary (i.e. claims data) data for assessing guideline adherence of CA. Moreover, transparent reporting, model validation, and various sensitivity analyses underpinned the results of this analysis.

Second, because validated and standardized approaches for assessing guideline adherence are not available, we evaluated guideline adherence based on a priori (self-) defined evaluating rules. Although these definitions are comprehensive and allow for standardized assessment, they are unlikely to exhaustively present the complex reality of the clinical practice. For instance, for some patients cCTA might be contraindicated due to obesity[43] or a stress-CMR due to pharmacological stressors and contrast agents.[44] However, our sensitivity analyses showed that even a smaller increase in guideline adherence (e.g. 70% guideline adherence) would still result in cost savings.

Third, in the 'adherent CA-use' arm the model did not distinguish between guideline-adherent and guideline non-adherent PCIs. This may have resulted in an unknown number of CAs which were classified as non-adherent, followed by a PCI (and thus overestimating the degree of guideline adherence in this arm). However, in a sensitivity analysis, a smaller increase in the level of guideline adherence (e.g. 70% only) would also result in lower costs and MACE per person compared to current practice (€1766 vs. €2206). Moreover, a meta-analysis of randomized-controlled trials showed that, for patients with SCAD, an initial revascularization strategy is not superior compared with an initial strategy without revascularization (regarding the risk of death, cardiac death, and myocardial infarction).[45]

Fourth, our analysis reflects a short time horizon (<1 year), thereby excluding future costs of diagnosis, potential revascularization, and cardiovascular events. However, evidence from

other trials showed no differences in ischemic cardiovascular events or deaths from any cause between initial PCI plus medical therapy and medical therapy alone over a median of 3.2 years,[46] and no difference in survival in a follow-up up to 15 years,[47] respectively. Therefore, the correct diagnosis with potential subsequent conservative therapy might be the focus for SCAD patients[48] and subject for future analyses when the long-term outcome data on diagnostic work-up are available.

Fifth, outpatient costs following a revascularization or no revascularization such as prescriptions or follow-up were excluded because 1-year costs have shown to be negligible (e.g. €21 for ASS[49] or €45-€80 for statins (e.g. atorvastatin)[50]) compared with other testing modalities or invasive procedures. Sensitivity analyses strengthened this assumption.

Finally, the model did not stratify for specific NIT, which would have required input data for clinical pathways (e.g. CA with prior NIT) conditional on the PTP-group and the applied NIT. However, this would have resulted in too small subgroups with increased uncertainty on cost-effectiveness.

Even though the beforehand mentioned limitations might limit our results to some extent, the recommendations of the current European Guidelines on the diagnosis and management of Chronic Coronary Syndrome 2019 (ESC)[26] rather support our conclusions. The current ESC includes updated PTP-values, which were reduced by approximately one-third compared to the previous version from 2013.[2] Based on these updated PTP-values, the ESC recommends an initial NIT w/o eECG for almost all patients (instead of a first-line CA for patients with a PTP of > 85% as in the prior version). Since the GNDMG is based on PTP-values from ESC 2013, the updated PTP-values according to ESC 2019 are lower than those from the ESC 2013. In ENLIGHT-KHK, guideline adherence according to the 2019 ESC guidelines was estimated at 21.3%. Sensitivity analyses showed that adopting the 2019 ESC guidelines would result in an even larger potential of improvement and cost savings (€866), and opposed to analyses based on GNDMG, also lead to costs savings for patients with a high PTP (€837).

Conclusion

The economic analysis in ENLIGHT-KHK indicates that improving guideline adherence for CA in patients with suspected SCAD would result in cost savings for the SHI in Germany. These findings can contribute to the design of incentive-based contract and reimbursement

models that may stimulate and strengthen a guideline-oriented and resource-efficient care in German healthcare setting.

Supplementary Material: Supplementary material is available at *European Heart Journal—Quality of Care and Clinical Outcomes* online.

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Authors' contributions: Y.S., B.W., O.B., and D.M. initiated the study. Y.S., D.M., and B.W. designed the decision-analytic model, acquired, analyzed and interpreted the data. Y.S. wrote the first draft of the manuscript. D.M. and B.W. revised the manuscript. O.B., S.L., J.A., S.S., and A.S. advised the analysis and interpretation of the data. All authors read and approved the final manuscript.

Data Availability Statement: The original data underlying this article cannot be shared publicly due to German data protection regulations. Aggregated data and the underlying model can be shared on reasonable request to the corresponding author.

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ENLIGHT-KHK registration details: German Clinical Trials Register DRKS00015638, Registered 19.02.2019**;** Universal Trial Number (UTN): U1111-1227-8055

Health Condition or Problem studied: ICD10: I20–Angina pectoris; ICD10: I25–Chronic ischaemic heart disease; ICD10: R07–Pain in throat and chest

References

1. Genders TSS, Steyerberg EW, Alkadhi H, et al. A clinical prediction rule for the diagnosis of coronary artery disease: validation, updating, and extension. *Eur Heart J* 2011;**32**:1316–1330.

2. Task Force M, Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C *et al.* 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J* 2013;**34**:2949–3003.

3. Bundesärztekammer (BÄK), Kassenärztliche Bundesvereinigung (KBV), Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF) 2019. *National disease management guidelines for chronic CAD (NVL)—long version*, 5th edition. www.khk.versorgungsleitlinien.de (10 February 23).

4. Deutsche Herzstiftung 2020. 32. Deutscher Herzbericht. https://www.herzstiftung.de/system/files/2021-06/Deutscher-Herzbericht-2020.pdf (10 February 23).

5. Mühlberger V, Kaltenbach L, Bates K, Ulmer H. Austrian National Cardiac Catheterization Laboratory Registry OKG: cardiac catherization in Austria: results from the Austrian National Cardiac Catheterization Laboratory Registry (ANCALAR) 2012- 2018. *Wien Klin Wochenschr* 2020;**132**:79–89.

6. Chmiel C, Reich O, Signorell A, Tandjung R, Rosemann T, Senn O. Appropriateness of diagnostic coronary angiography as a measure of cardiac ischemia testing in non-emergency patients—a retrospective cross-sectional analysis. *PLoS One* 2015;**10**:e0117172.

7. Figulla HR, Lauten A, Maier LS, Sechtem U, Silber S, Thiele H. Percutaneous coronary intervention in stable coronary heart disease—is less more? *Dtsch Arztebl International* 2020;**117**:137–144.

The content of dissertation project III has been published in Eur Heart J Qual Care Clin Outcomes

8. Möckel M, Searle J, Jeschke E. *Indikation, prognose und regionale unterschiede der herzkatheterversorgung in Deutschland*. 1 edn .In: *Versorgungs-Report 2013/2014.* eds. J Klauber, C Günster, B Gerste, B-P Robra and N Schmacke. Stuttgart: Schattauer; 2014, p231–254.

9. Dissmann W, De Ridder M. The soft science of German cardiology. *Lancet* 2002;**359**:2027–2029.

10. Piedmont S, Swart E, Kenmogne R, Braun-Dullaeus RC, Robra B-P. [Left-heart catheterization followed by other invasive procedures: regional comparisons reveal peculiar differences]. *Z Evid Fortbild Qual Gesundhwes* 2017;127–128:62–71.

11. Frank-Tewaag J, Bleek J, Günster C, et al. Regional variation in coronary angiography rates: the association with supply factors and the role of indication: a spatial analysis. *BMC Cardiovasc Disord* 2022;**22**:72.

12. Institute for Quality Assurance and Transparency in Healthcare (IQTiG) 2021. Bundesqualitätsbericht 2021. QS-verfahren perkutane koronarintervention (PCI) und koronarangiographie. Erfassungsjahre 2019 und 2020. https://iqtig.org/veroeffentlichungen/bundesqualitaetsbericht/ (22 December 22).

13. Timmis A, Vardas P, Townsend N, et al. European Society of Cardiology: cardiovascular disease statistics 2021. *Eur Heart J* 2022;**43**:716–799.

14. Baldus S, Werdan K, Levenson B, Kuck KH. Klug entscheiden:... in der Kardiologie. *Dtsch Arztebl International* 2016;**113**:1312–1315.

15. Seleznova Y, Wein B, Müller D, et al. Evaluation of guideline adherence for cardiac catheterization in patients with presumed obstructive coronary artery disease in Germany (ENLIGHT-KHK) - a multicentre, prospective, observational study. *Cardiovasc Revasc Med* 2021;**31**:19–25.

16. Al-Hijji MA, Lennon RJ, Gulati R, et al. Safety and risk of major complications with diagnostic cardiac catheterization. *Circ Cardiovasc Interv* 2019;**12**:e007791.

17. Briggs AH, O'brien BJ. The death of cost-minimization analysis? *Health Econ* 2001;**10**:179–184.

18. Husereau D, Drummond M, Augustovski F, et al. Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) statement: updated reporting guidance for health economic evaluations. *BMJ* 2022;**376**:e067975.

19. Kaiser C, Brunner-La Rocca HP, Buser PT, et al. Incremental cost-effectiveness of drug-eluting stents compared with a third-generation bare-metal stent in a real-world setting: randomised Basel Stent Kosten Effektivitats Trial (BASKET). *Lancet* **2005**;366:921–929.

20. Rocca HPB-La, Kaiser C, Bernheim A, et al. Costeffectiveness of drug-eluting stents in patients at high or low risk of major cardiac events in the Basel Stent KostenEffektivitats Trial (BASKET): an 18-month analysis. *Lancet* 2007;**370**:1552–1559.

The content of dissertation project III has been published in Eur Heart J Qual Care Clin Outcomes

21. Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. *Methods for the Economic Evaluation of Health Care Programmes*. 4th ed. Oxford: Oxford University Press; 2015.

22. Garrison LP, Pauly MV,Willke RJ, Neumann PJ. An overview of value, perspective, and decision context-A health economics approach: an ISPOR Special Task Force report [2]. *Value Health* 2018;**21**:124–130.

23. Institute for Quality and Efficiency in Health Care (IQWiG) 2022, General Methods Version 6.1. https://www.iqwig.de/methoden/allgemeine-methoden-v6-1.pdf (22 December 22).

24. Kolkailah AA, Alreshq RS, Muhammed AM, Zahran ME, Anas El-Wegoud M, NabhanAF. Transradial versus transfemoral approach for diagnostic coronary angiography and percutaneous coronary intervention in people with coronary artery disease. *Cochrane Database Syst Rev* 2018;**4**:CD012318.

25. Davis S, Stevenson M, Tappenden P, Wailoo AJ. The National Institute for Health and Care Excellence (NICE) Decision Support Unit, Technical Support Document 15: cost-effectiveness modelling using patient-level simulation. 2014. https://www. sheffield.ac.uk/media/34206/download?attachment (22 December 22).

26. Knuuti J,Wijns W, Saraste A, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J* 2020;**41**:407–477.

27. Diamond GA, Forrester JS. Analysis of probability as an aid in the clinical diagnosis of coronary-artery disease. *N Engl J Med* 1979;**300**:1350–1358.

28. Briggs A, Claxton K, Sculpher M. *Decision modelling for health economic evaluation*. Reprint. edn. Oxford: Oxford University Press; 2011.

29. Juarez-Orozco LE, Saraste A, Capodanno D, et al. Impact of a decreasing pre-test probability on the performance of diagnostic tests for coronary artery disease. *Eur Heart J Cardiovasc Imaging* 2019;**20**:1198–1207.

30. German Diagnosis Related Groups (G-DRG), Version 2022. https://www.g-drg.de/ aG-DRG-System_2022 (10 Feb 2023).

31. German Uniform Assessment Standard (EBM). https://www.kbv.de/html/ arztgruppen_ebm.php#content2398 (10 Feb 2023).

32. Hospital Association North Rhine-Westphalia (KGNW) 2022. *Contract according to § 115 paragraph 2 nr. 4, Volume V of the German Social Security Code*. https://www.kgnw. de/download/dl-vs-ns-behandlungen-verguetung.pdf. (10 February 2023).

33. Federal Statistics Office (Destatis) 2022. https://www-genesis.destatis.de/genesis/ online?sequenz = tabelleErgebnis&selectionname = 61111-0004&sachmerkmal = CC13A5&sachschluessel = CC13-06∗&zeitscheiben = 3#abreadcrumb (22 December 22).

The content of dissertation project III has been published in Eur Heart J Qual Care Clin Outcomes

34. Moschetti K, Kwong RY, Petersen SE, et al. Cost-minimization analysis for cardiac revascularization in 12 health care systems based on the EuroCMR/SPINS registries. *JACC Cardiovasc Imaging* 2022;**15**: 607–625.

35. Nazir MS, Rodriguez-Guadarrama Y, Rua T, et al. Cost-effectiveness in diagnosis of stable angina patients: a decision-analytical modelling approach. *Open heart* 2022;**9**:e001700.

36. Vemer P, Corro Ramos I, Van Voorn GAK, Al MJ, Feenstra TL. AdViSHE: a validation-assessment tool of health-economic models for decision makers and model users. *Pharmacoeconomics* 2016;**34**:349–361.

37. Reimbursement Institute 2022. https://app.reimbursement.info/drgs/F49G (22 December 22).

38. Cabana MD, Rand CS, Powe NR, et al. Why don't physicians follow clinical practice guidelines? A framework for improvement. *JAMA* 1999;**282:**1458–1465.

39. Gurses AP, Marsteller JA, Ozok AA, Xiao Y, Owens S, Pronovost PJ. Using an interdisciplinary approach to identify factors that affect clinicians' compliance with evidence-based guidelines. *Crit Care Med* 2010;**38**:S282–S291.

40. Correa VC, Lugo-Agudelo LH, Aguirre-Acevedo DC, et al. Individual, health system, and contextual barriers and facilitators for the implementation of clinical practice guidelines: a systematic metareview. *Health Res Policy Syst* 2020;**18**:74.

41. Hoorn CJGM, Crijns HJGM, Dierick-Van Daele ATM, Dekker LRC. Dekker LRC Review on factors influencing physician guideline adherence in cardiology. *Cardiol Rev* 2019;**27**:80–86.

42. Herwig A, Dehnen D, Weltermann B. Patient factors driving overuse of cardiac catheterisation: a qualitative study with 25 participants from two German teaching practices. *BMJ open* 2019;**9**:e024600.

43. Gueret P, Deux JF, Bonello L et al. Diagnostic performance of computed tomography coronary angiography (from the Prospective National Multicenter Multivendor EVASCAN Study). *Am J Cardiol* 2013;**111**: 471–478.

44. Knuuti J, Bengel F, Bax JJ et al. Risks and benefits of cardiac imaging: an analysis of risks related to imaging for coronary artery disease. *Eur Heart J* 2014;**35**:633–638.

45. Chacko L, Howard JP, Rajkumar C, et al. Effects of percutaneous coronary intervention on death and myocardial infarction stratified by stable and unstable coronary artery disease: a meta-analysis of randomized controlled trials. *Circ Cardiovasc Qual Outcomes* 2020;**13**:e006363.

46. Maron DJ, Hochman JS, Reynolds HR, et al. Initial invasive or conservative strategy for stable coronary disease. *N Engl J Med* 2020;**382**:1395–1407.

47. Sedlis SP, Hartigan PM, Teo KK, et al. Effect of PCI on long-term survival in patients with stable ischemic heart disease. *N Engl J Med* 2015;**373**:1937–1946.

The content of dissertation project III has been published in Eur Heart J Qual Care Clin Outcomes

48. Al-Lamee RK, Foley M, Rajkumar CA, Francis DP. Revascularization in stable coronary artery disease. *BMJ* 2022;**377**:e067085.

49. Lamy A, Eikelboom J, Tong W, et al. The costeffectiveness of Rivaroxaban with or without aspirin in the COMPASS trial. *Eur Heart J Qual Care Clin Outcomes* 2022; Aug 24: qcac054.

50. Die Kassenärztliche Vereinigung und die Verbände der Krankenkassen in Niedersachsen 2022. https://www.kvn.de/internet_media/Mitglieder/Verordnungen/Arzneimittel/Ver%C3%B6ffentlichungen/Rezept_Info_+Lipidsenker-p-2002.pdf (10 February 23).

Chapter 8 Dissertation project IV: Subgroup analysis

Evaluation of the guideline-adherence of coronary angiography in patients with suspected chronic coronary syndrome – Results from the German prospective multicentre ENLIGHT-KHK project

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Abstract

Background: With 900′ 000 coronary angiographies (CA) per year, Germany has the highest annual per capita volume in Europe. Until now there are no prospective clinical data on the degree of guideline-adherence in the use of CA in patients with suspected chronic coronary syndrome (CCS) in Germany.

Methods: Between January 2019 and August 2021, 458 patients with suspected CCS were recruited in nine German centres. Guideline-adherence was evaluated according to the current European Society of Cardiology and German guidelines. Pre-test probability (PTP) for CAD was determined using age, gender, and a standardized patient questionnaire to identify symptoms. Data on the diagnostic work-up were obtained from health records.

Results: Patients were in mean 66.6 years old, male in 57.3%, had known CAD in 48.4% and presented with typical, atypical, non-anginal chest pain or dyspnoea in 35.7%, 41.3%, 23.0% and 25.4%, respectively. PTP according to the European guidelines was in mean 24.2% (11.9%-36.5% 95% CI). 20.9% of the patients received guideline-recommended preceding non-invasive image guided testing. The use of CA was adherent to the European and German guideline recommendations in 20.4% and 25.4%, respectively. In multivariate analysis, arterial hypertension and prior revascularization were predictors of guideline non-adherence.

Conclusion: These are the first prospective clinical data which demonstrated an overall low degree of guideline-adherence in the use of CA in patients with suspected CCS in the German health care setting. To improve adherence rates, the availability of and access to non-invasive image guided testing needs to be strengthened. (German Clinical Trials Registry DRKS00015638 – Registration Date: 19.02.2019)

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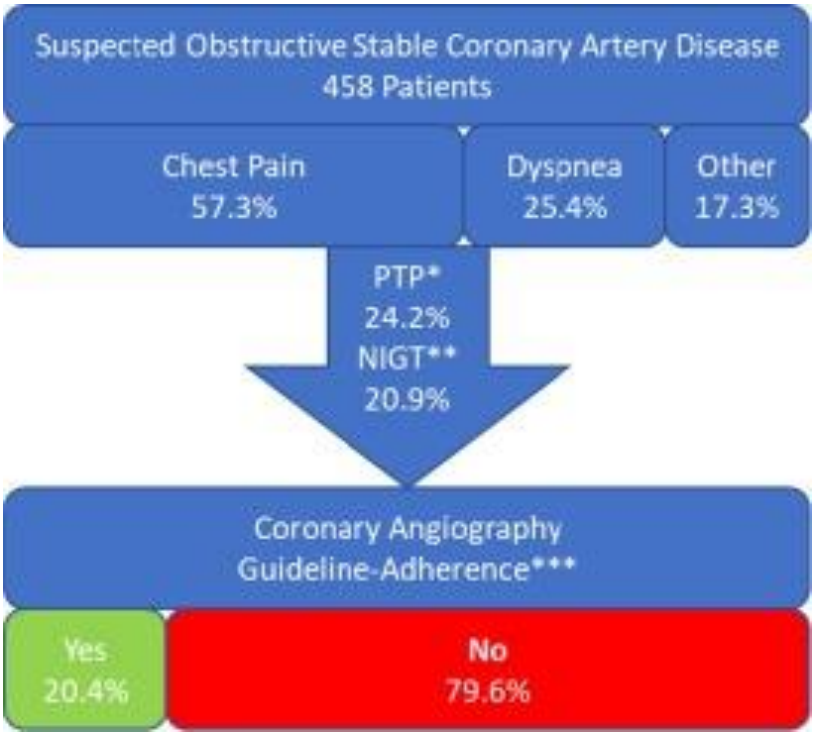
Graphical abstract

Patients with suspected obstructive stable coronary artery disease undergoing coronary angiography included in the trial with presenting symptoms, mean pre-test probability (PTP) (according to the 2019 European Society of Cardiology guidelines on chronic coronary syndrome) and prior non-invasive image guided testing (NIGT) and the respective proportion of guideline-adherent and non-adherent coronary angiographies in this population. *PTP – pre-test probability; **NIGT – non-invasive image guided testing; *** according to the 2019 European Society of Cardiology guidelines on chronic coronary syndrome.



Keywords: Guideline adherence, Chronic coronary syndrome, Coronary angiography, Angina pectoris, Coronary artery disease

Abbreviations: ACS, Acute Coronary Syndrome; CA, Coronary Angiography; CAD, Coronary Artery Disease; CCS, Chronic Coronary Syndrome; CI, Confidence Interval; ESC, European Society of Cardiology; ESC-CCS-GL, 2019 European Society of Cardiology Guidelines on Chronic Coronary Syndrome; GL, Guideline; GNM-GL, German National Disease Management Guideline on Chronic Coronary Artery Disease; NIGT, Non-invasive Image Guided Testing; PCI, Percutaneous Coronary Intervention; PTP, Pre-test Probability; SHI, Statutory Health Insurance.

The content of dissertation project IV has been published in Int J Cardiol Heart Vasc

Introduction

The 2019 European Society of Cardiology (ESC) Guidelines (GL) for the diagnosis and management of Chronic Coronary Syndrome (ESCCCS-GL) and the German National Disease Management GL on chronic coronary artery disease (GNM-GL) (which is based on the 2013 ESC-GL on the management of stable coronary artery disease (CAD)) recommend an algorithmic, symptom and pre-test probability (PTP) based approach for the diagnostic work-up of patients with suspected symptomatic obstructive CAD in chronic coronary syndrome (CCS)[1–3]. According to this approach, non-invasive image guided testing (NIGT) with either stress-echocardiography, myocardial perfusion scintigraphy, coronary CT-angiography or stress cardiac magnetic resonance imaging is recommended for the majority of patients[1,2].

In Germany up to 900 000 coronary angiographies (CA) are performed per year, thereof approximately 500 000 in patients with suspected CCS[4,5]. With around 1 100 CA in 100 000 citizens per year, Germany has the highest annual per capita volume in Europe, 1.7 times higher than second placed Austria[4,6]. According to the German national annual quality assurance report 60% of CA in patients with suspected obstructive CAD have objective signs of ischemia. However, international and interregional differences in per capita volumes of CA are considered noteworthy indicators of a potential overuse of CA in Germany[4,5,7–9]. Health claims data-based analyses found considerable interregional differences in CA rates in Germany, especially in patients with suspected CCS but not in those with acute myocardial infarction[8,9]. This hints to a significant relationship between regionally available capacities and the (over-) use of CA in the diagnostic work-up for stable CAD[8]. Albeit the longstanding discussion and results of health claims data-based analyses, until now there are no prospective German clinical data on the degree of GL-adherence in the use of CA in patients with suspected obstructive stable CAD[10].

The ENLIGHT-KHK health-care research project (i) prospectively evaluated the degree of GL-adherence, (ii) assessed health economic consequences of potential deviations in GL-adherence and (iii) evaluated potential facilitators or barriers of GL-adherent decision making. The rationale, the trial design and the objectives of the project were published before[11].

This study presents the results of the evaluation of GL-adherence in the use of CA in the predefined cohort of patients with suspected CCS. Furthermore, differences in the rate of GL-

adherence between the latest ESC-CCS-GL and the GNM-GL, which are based on the 2013 ESC-GL on stable CAD, were evaluated[1–3].

Methods

Study design

ENLIGHT-KHK was a prospective, observational, multicentre trial in the German federal states of North Rhine-Westphalia and Hamburg which recruited consecutive patients who were insured by the statutory health insurance (SHI) companies AOK Rheinland-Hamburg and AOK NORDWEST. The nine participating centres were all non-university hospitals providing 24/7 catheterization laboratory services for the care of acute myocardial infarctions as well as elective in- or outpatient diagnostic CA. Per Hospital, in mean 1 880 CA are performed per year (range 830 to 4 500, median 1 330). All patients gave written informed consent. The study was conducted according to the declaration of Helsinki, approved by the local ethics committees, and registered in the German Clinical Trials Registry (DRKS00015638).

Study population

Patients with clinical suspicion of CCS without acute myocardial infarction were included into one of five predefined cohorts – two main (1 and 2) and three sub-cohorts (3, 4 and 5). The distinct cohorts were defined by clinical setting and the respective step of the diagnostic workup at which the patients were included. These cohorts were: (i) patients referred for elective CA, (ii) patients presenting at the emergency department who underwent CA, (iii) patients presenting in the outpatient department without prior diagnostic work-up, (iv) patients presenting at the emergency department undergoing planned non-invasive testing, and (v) patients referred for elective NIGT. Patients with heart failure and a left ventricular ejection fraction below 40% were excluded. Periprocedural complications (access-site related bleeding, myocardial infarction, stroke, or death) were taken from health records, after discharge complications were followed up with patient-level health claims data for 30 days.

For this study all patients in cohort 1 were included in the analysis (see Fig. 1 for details).

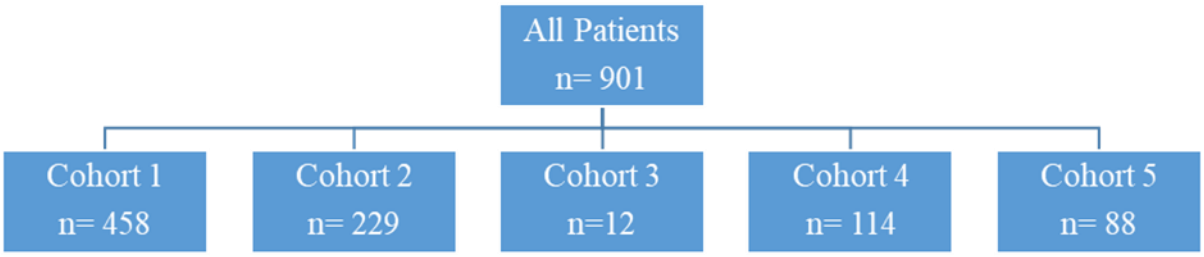


Figure 1: Number of patients with clinical suspicion of obstructive coronary artery disease without acute myocardial infarction who were included in the study and grouped into five predefined cohorts – two main (1 and 2) and three sub-cohorts (3, 4 and 5). The distinct cohorts were: (i) patients undergoing elective coronary angiography, (ii) patients primarily presenting at the emergency department who underwent coronary angiography, (iii) patients presenting in the outpatient department, (iv) patients presenting at the emergency department undergoing planned non-invasive and (v) patients presenting for elective non-invasive image guided testing.

Definition of guideline adherence and data collection

We assessed GL-adherence of CA according to the recommendations of the ESC-CCS-GL (which is endorsed by the German National Cardiac Society (DGK)) and the GNM-GL[1,2,12]. For this purpose, the diagnostic work-up and the PTP of obstructive CAD were determined at patient-level.

The information on the diagnostic work-up before CA, especially on NIGT, were taken from the patients' health records. To obtain the nature of symptoms and level of exercise capacity without physician bias, they were collected by a self-designed standardized patient questionnaire.

Symptoms were categorized into typical angina, atypical angina, nonanginal chest pain or dyspnoea using the definitions and wording of the ESC-CCS-GL and GNM-GL, respectively (see appendix chapter 13.1 for details on the patient questionnaire and the evaluating rules to define the symptom categories)[1,2]. The PTP was then determined using age, gender and the main symptom according to the respective tables of the ESC-CCS-GL and the GNM-GL (see appendix Table A 1 and Table A 2 for details on the respective PTP-tables)[1,2]. In case of concomitant chest pain and dyspnoea, the higher PTP value was applied. The GNM-GL define the PTP values as published in the 2013 ESC-GL on the management of stable CAD[1–3]. The PTP-based recommendations for the diagnostic work-up of the respective GL are summarized in Table 1.

Table 1: Summary of the pretest-probability based recommendations for the diagnostic work-up of patients with suspected chronic coronary syndrome

2019 European Society of Cardiology Guideline on Chronic Coronary Syndrome [2]	**German National Disease Management Guideline on Stable Coronary Artery Disease[1]**	**Recommendation according to the respective guideline**
Pre-test Probability	Pre-test Probability	
Low <5%	Low <15%	No further testing
Low Intermediate 5-15%	Intermediate 15-85%	Non-invasive image-guided testing***;
*Intermediate >15%**		Coronary angiography in case of evidence of ischemia or stenosis
n.a.**	High >85%	Direct coronary angiography

Summary of pre-test probability based recommendations for the diagnostic work-up of the 2019 European Society of Cardiology Guidelines for the diagnosis and management of chronic coronary syndrome and the German National Disease Management Guideline on chronic coronary artery disease for patients with suspected obstructive stable coronary artery disease[1,2]. * Decision for diagnostic work-up depends on clinical judgement; ** not applicable, highest possible value is 52%; ***Stress-echocardiography, coronary computed tomography angiography, myocardial perfusion scintigraphy or cardiac stress magnet resonance imaging depending on clinical likelihood, availability, and local expertise.

GL-adherence of CA was evaluated based on the a-priori defined rules outlined in Table 2 (see appendix table A 3 for details on the evaluating rules and definitions of GL-adherence). To respect the clinical judgement of the treating physicians, the indication of a CA in patients with a PTP > 5% and an inconclusive finding in NIGT or with a PTP < 5% but with evidence of ischemia, stenosis, or an inconclusive finding in NIGT was considered GL-adherent, too.

Table 2: Assessment of guideline-adherence of coronary angiography depending on pretest probability (PTP) and results of non-invasive image guided testing

Pre-Test Probability*	**Non-Invasive Image Guided Testing**	**Guideline-Adherence of Coronary Angiography**
Low	Not done or non-pathological	No
	Pathological or inconclusive	Yes
Intermediate	Not done or non-pathological	No
	Pathological or inconclusive	Yes
High	Irrespective of non-invasive testing	Yes

Assessment of guideline-adherence of coronary angiography depending on pre-test probability (PTP) and the results of non-invasive image guided testing (Stress-Echo, Myocardial Perfusion Scintigraphy, Coronary CT Angiography or Stress-MRI).* PTP was defined as low at < 5% and < 15% according to the 2019 European Society of Cardiology guideline for the diagnosis and management of chronic coronary syndrome and the German National Disease Management Guideline on chronic coronary artery disease, respectively, intermediate at > 5% and 15–85%, respectively, and high at > 85%1,2.

Statistics

Continuous variables are presented as mean and standard deviation while categorical variables are summarized as frequencies and percentages. The normal distribution of continuous variables was assessed using the Shapiro–Wilk test. If normally distributed, variables were compared using the Student's t-test, otherwise the Wilcoxon rank-sum test was used. Categorical variables were compared using the Chisquare test or Fisher's exact test, if appropriate. The association between guideline adherence and a set of covariates was assessed using logistic regression analysis. Covariates were factors potentially influencing the clinical likelihood and therefore decision making, e.g. age, gender, known history of CAD and arterial hypertension as well as country of origin (because patients with migratory background might confer a higher risk of inappropriate treatment)[2,13]. Furthermore, the referral pattern (especially referral by cardiologists or general practitioners) was used as differences in expertise might influence guideline adherence. Both uni- and multivariable analyses were conducted. Results of logistic regression are presented as odds ratio (OR) and the corresponding 95% confidence interval (CI). All tests were two tailed and a p-value < 0.05 was considered as the threshold of statistical significance. All analyses were conducted in R, version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria).

The content of dissertation project IV has been published in Int J Cardiol Heart Vasc

Results

Patients' characteristics

Overall, 901 patients were recruited in nine centres between January 2019 and August 2021. In this study cohort (cohort 1) 458 patients being referred for CA in suspected CCS were included. They were in mean 66.6 years old and male in 57.3%. Furthermore, patients were at increased cardiovascular risk due to known arterial hypertension (83.5%) or known CAD with prior revascularization (48.4%) and they were most often referred by cardiologists (58.8%) or family doctors (18.3%) (see Table 3 for details).

Table 3: Baseline Characteristics of patients in total and with guideline-adherent and guideline non-adherent coronary angiography

Parameter	Statistic	Total	Guideline-Adherent Coronary Angiography	Guideline Non-Adherent Coronary Angiography	p-value
Total	n	458			
Guideline-Adherence determined	n/N (%)	426/458(93.0)	87/426 (20.4)	339/426 (79.6)	
Age (years)	Mean (SD)	66.63 (10.37)	65.09 (8.4)	67.03 (10.8)	0.120
Gender male	n/N (%)	244/426 (57.3)	55/87 (63.2)	189/339(55.8)	0.257
BMI kg/m²	Mean (SD)	29.85 (5.8)	29.66 (5.7)	29.90 (5.9)	0.736
Cardiovascular Risk Factors					
Arterial Hypertension	n/N (%)	353/423 (83.5)	61/86 (70.9)	292/337 (86.6)	0.001
Hypercholesterolaemia /Dyslipidaemia	n/N (%)	239/420 (56.9)	46/86 (53.5)	193/337 (57.8)	0.552
Diabetes Mellitus					0.612
Type I	n/N (%)	3/429 (0.7)	0/92 (0.0)	3/337 (0.9)	
Type II	n/N (%)	138/421 (32.8)	27/87 (31.0)	111/334 (33.2)	
Current Smoker	n/N (%)	111/396 (28.0)	21/79 (26.6)	90/317 (28.4)	0.658
Family history of CAD	n/N (%)	145/355 (40.8)	29/69 (42.0)	116/286 (40.6)	0.931
Cardiac History					
Prior MI	n/N (%)	80/424 (18.9)	7/86 (8.1)	73/338 (21.6)	0.007
Known CAD with prior Revascularization	n/N (%)	206/426 (48.4)	26/87 (29.9)	180/339 (53.1)	<0.001
Prior PCI	n/N (%)	171/426 (40.1)	18/87 (20.7)	153/339 (45.1)	<0.001
Prior CABG	n/N (%)	39/424 (9.2)	9/87 (10.3)	30/337 (8.9)	0.824
Atrial Fibrillation	n/N (%)	70/426 (16.4)	11/87 (12.6)	59/339 (17.4)	0.365
Non-cardiac Medical History					
Chronic Obstructive Lung Disease	n/N (%)	48/424 (11.3)	12/87 (13.8)	36/337 (10.7)	0.525
Chronic renal insufficiency*	n/N (%)	32/427 (7.5)	5/87 (5.7)	27/339 (8.0)	0.637
Stroke	n/N (%)	39/424 (9.2)	4/87 (4.6)	35/337 (10.3)	0.149
Peripheral/ Vascular Disease	n/N (%)	39/424 (9.2)	5/87 (5.7)	34/337 (10.1)	0.304
Referred by					0.990
Family doctor	n/N (%)	76/415 (18.3)	16/86 (18.6)	60/329 (18.2)	
Specialist (cardiology)	n/N (%)	244/415 (58.8)	50/86 (58.1)	194/328 (59.0)	
Other	n/N (%)	95/415 (22.9)	20/86 (23.3)	75/329 (22.8)	

Baseline Characteristics of patients in total and with guideline-adherent and guideline non-adherent coronary angiography according to the 2019 European Society of Cardiology guideline for the diagnosis and management of chronic coronary syndrome.2 Due to missing data, guideline-adherence could not be determined in 32 of 458 (7.0%) of patients. If numbers do not equal the total number of patients, it is because of missing data. *Defined as an estimated glomerular filtration rate < 60 ml/min/1,72 m2. CABG, Coronary Artery Bypass Grafting; CAD, Coronary Artery Disease; PCI, Percutaneous Coronary Intervention.

Presenting symptoms and diagnostic work-up

The patients' main symptoms (based on the questionnaire) were chest pain, shortness of breath and exercise intolerance in 57.3%, 25.4% and 9.6%, respectively. Specifically asked for angina, symptoms were categorized in typical angina, atypical angina or non-anginal chest pain in 35.7%, 41.3% and 23.0% respectively. Exercise tolerance level according to the Canadian Cardiovascular Society grading was class 1–2 in 49.8% and class 3–4 in 43.1%. Prior to CA, patients underwent NIGT in 20.9% with stress-echocardiography, stress cardiac magnetic resonance imaging, myocardial perfusion scintigraphy and coronary CT-angiography in 1.9%, 4.2%, 8.2 and 7.0%, respectively. Two patients received coronary CT-angiography followed by GL-recommended functional testing. Exercise-ECG was performed in 18.5% of patients (see Table 4 for details and appendix table A 4 for further details on noninvasive testing).

Table 4: Result of the type of main complaints, non-invasive and invasive testing of patients in total and with guideline-adherent and guideline non-adherent coronary angiography

Parameter	Statistic	Total	Guideline-Adherent Coronary Angiography	Guideline Non-Adherent Coronary Angiography	p-value
Main Complaint*					
Chest Pain	n/N (%)	244/426 (57.3)	49/87 (56.3)	195/339 (57.5)	0.780
Shortness of Breath	n/N (%)	108/425 (25.4)	26/87 (29.9)	82/338 (24.2)	
Exercise Intolerance	n/N (%)	41/427 (9.6)	7/87 (8.0)	34/340 (10.0)	
Other complaints	n/N (%)	27/426 (6.3)	4/87 (4.6)	23/339 (6.8)	
Angina pectoris*					
Typical Angina	n/N (%)	152/426 (35.7)	25/87 (28.7)	127/339 (37.5)	0.155
Atypical Angina	n/N (%)	176/426 (41.3)	36/87 (41.4)	140/339 (41.3)	
Non-Anginal Chest Pain	n/N (%)	98/426 (23.0)	26/87 (29.9)	72/339 (21.2)	
Non-invasive Testing and Revascularization					
Non-Invasive Image Guided Testing	n/N (%)	89/426 (20.9)	84/87 (96.6)	5/339 (1.5)	<0.001
Revascularization	n/N (%)	177/426 (41.5)	42/87 (48.3)	135/339 (39.8)	0.192

Result of the type of main complaints, non-invasive and invasive testing of patients in total and with guideline-adherent and guideline non-adherent coronary angiography according to the 2019 European Society of Cardiology Guideline for the diagnosis and management of chronic coronary syndrome2. * Based on the patient questionnaire.

Based on the questionnaire the patients' PTP was in mean 24.2% (11.9 – 36.5%, 95% CI) according to the ESC-CCS-GL and 54.3% (32.4 – 76.2%, 95% CI) according to the GNM-GL. Patient specific PTP was documented by the treating physician in the health records in 5.9% of

the cases. Due to missing values in the patient questionnaire, the GL-adherence could not be estimated for 32 of 458 (7.0%) patients.

Guideline-adherence of CA

Among the study population, 20.4% of the CAs were GL-adherent according to the ESC-CCS-GL and 25.4% according to the GNM-GL. In particular, GL-adherence according to the ESC-CCS-GL was achieved in 84 of 87 patients (96.6%) by conducting a NIGT prior to the CA. Three patients had class 3 angina, two with a pathologic exercise-ECG and one with a pathologic echocardiography at rest (both scenarios defined as high-risk situations in the ESC-CCS-GL allowing direct referral for CA). GL non-adherence was the result of CA in patients with no signs of ischemia or stenosis in NIGT in 5 of 339 patients (1.5%) and the absence of a recommended prior NIGT in 334 of 339 patients (98.5%). GNM-GL adherence in 31 of 429 (7.2%) patients was due to a PTP > 85% with a consecutive indication for direct CA without prior NIGT. In this group, nine patients (2.2%) received an additional NIGT although their PTP was > 85%.

Results and consequences of the CA

CA found a coronary one, two and three vessel disease in 18.5%, 18.1% and 28.4%, respectively, coronary sclerosis in 11.7% or excluded CAD in 19.5%. Fractional flow reserve was performed in 8.0% of the patients. A proportion of 41.5% of patients underwent revascularization with 89.2% percutaneously and 10.8% with planned bypass surgery. Revascularization was more likely to be performed in the GL-adherent group, but without reaching a significant difference (48.3% vs. 39.8%, p = 0.192) (see appendix table A 5 for details).

Among the 458 CA, only few periprocedural complications were reported – one myocardial infarction, one coronary artery dissection and eight conservatively treated access site complications.

Factors associated with guideline-adherence

While known CAD with prior revascularization (OR 0.40, 0.23–0.67 95% CI, p = 0.001) and arterial hypertension (OR 0.38, 0.22–0.66 95% CI, p = 0.007) were predictive of GL non-adherence, other factors including age, gender, non-German origin, referral by family doctor or

cardiologist were not significantly associated with guideline adherence in the multivariate logistic regression analyses.

Discussion

These are the first prospective multicentre data to evaluate the GL-adherence in the use of CA in patients with suspected obstructive CAD in Germany. According to the ESC-CCS 2019 GL and the GNM-GL, the degree of GL-adherence was 20.4% and 25.4%, respectively.

The study population was a contemporary population recruited in nine different centres in North Rhine Westphalia and Hamburg. The centres were all non-university hospitals providing elective CA capacities as well as 24/7 services for patients with acute myocardial infarctions. In Germany CA are conducted by 1 078 health care providers in general, and 770 non-university and 43 university hospitals in specific, with a median annual volume of 1 000 to 1 499 CA per health care provider[5,14]. With 830 to 4 500 (in median 1 330) CA per year the participating study centres reflect a representative spectrum of health care providers.

The ENLIGHTK-KHK population was slightly younger (66.3 vs. 68.5 years), but more obese (BMI 29.9 vs. 28.2 kg/m2) and had a higher proportion of women (42.7% vs. 36.1%) than the German national quality assurance cohort of patients undergoing CA for suspected CCS[5]. Compared to a sample of 4 500 patients undergoing elective CA at the Luxembourg Heart Institute published by Tchicaya et al., our study population had a higher clinical likelihood for CCS with a higher prevalence of arterial hypertension (83.5% vs. 68.1%), diabetes mellitus type II (32.8% vs. 29.1%) and current smoking status (28.0% vs. 22.2%), but a lower rate of hypercholesterolemia (56.9% vs. 64.4%)[15]. This might hint for a pre-selection of patients in this study population in a way that patients with a higher clinical likelihood were more likely to be referred for direct CA. Despite a higher clinical likelihood, NIGT prior to CA would have been GL-recommended for the majority of patients.

While according to the ESC-CCS-GL only 10–15% of patients with suspected stable CAD present with typical angina, in our study population this proportion was 35.7%[2]. The difference might be explained by the clinical judgement of the involved physicians, who might preferably have referred patients with typical angina for direct CA. Especially patients with prior revascularization or arterial hypertension were more likely to undergo direct CA, assumingly as they were attributed a higher clinical likelihood of obstructive CAD[2]. Arterial hypertension

may furthermore mimic clinical symptoms similar to those of coronary ischaemia which may induce physicians to directly transfer those patients to CA (i.e. without prior NIGT).

In our study population a proportion of 20.9% underwent the ESCCCS-GL-recommended NIGT prior to CA, an additional 18.5% of patients at least received an exercise-ECG. These findings are in direct contrast to the results of the mandatory German national quality assurance program. Therein the indicator "objective signs of ischemia" was documented in 60% of patients without acute coronary syndrome undergoing CA[5]. Objective signs were defined as pathologic exercise- ECG, resting-echocardiography, stress-echocardiography, myocardial perfusion scintigraphy, coronary CT-angiography or stress cardiac magnetic resonance imaging[5]. This discrepancy might be explained by a high proportion of patients who underwent the widely available exercise-ECG or even a certain degree of misdocumentation in order not to breach quality thresholds. According to the "Herzbericht 2020" there are no specific data on the numbers and availability of NIGT in Germany and therefore the assumption of higher rates of NIGT outside the trial centres cannot not be verified[14]. Instead, the authors of the European DISCHARGE-trial report functional testing with pathologic or nondiagnostic results prior to CA in an intermediate PTP cohort in 18%, which would meet the ENLIGHT-KHK definition of GL-adherent use of CA[16]. Their findings support the validity of the reported GL adherence rates in this study. To increase the quality of indication for diagnostic CA in CCS the mandatory quality assurance program needs to put emphasis on collecting reliable data on the use of NIGT and the patients' PTP.

With a revascularization rate of 39.8% in patients without prior NIGT in our study population (and thus no objective signs of ischemia), the appropriateness of PCI in Germany may be questioned, too, as done by Figulla et al.[4]. The importance to appropriately select patients for CA is outlined by Bradley et al. who showed that inappropriate CA seem to be a significant trigger of inappropriate revascularizations (data of the US national cardiovascular registry)[17]. Despite CA not being GL-adherent in the majority of cases, our study confirmed that diagnostic CA is a safe method with a low rate of intra- and perioperative complications, which is in line with current literature[18].

Using the ESC-CCS-GL only 20.4% of CA were considered GL-adherent, while in almost four-fifths of patients they were not. Among the 87 GL-adherent patients 96.6% had prior NIGT with at least an inconclusive finding, the remaining presented with clinical high-risk situations. In the GL non-adherent patients, exercise-ECG was performed in 18.0% and echocardiography

at rest in 81.7%, but no NIGT in 98.5%. Five patients underwent CA without evidence of ischemia in NIGT, most likely because a false-negative result of NIGT was taken into consideration. While there were no other clinical data on the GL-adherence for Germany, for Switzerland Chmiel et al. reported preceding NIGT in the same range as our study (15.2% of 2.714 patients undergoing elective CA)[19]. They also showed that the rate of NIGT prior to elective CA may be influenced by managed care health insurance models and therein be increased up to 37%[20]. Given the total number of CA in Germany for suspected obstructive CAD in CCS (about 500 000 per year) the proportion of 20.4% of GL-adherent CA would mean nearly 400 000 non-adherent CA[4,5]. To at least achieve a GL-adherence rate of e.g. the above mentioned 37% in Germany, the annual numbers of NIGT nearly need to be doubled up to an additional 83 000 NIGT per year.

The reduction of the PTP-values in the ESC-CCS-GL compared to the 2013 ESC-GL on the management of stable CAD (on which the GNM-GL refer to) lead to a change from GL-adherence to GL non-adherence in this cohort[1–3]. While the ESC-CCS-GL recommend NIGT for almost all patients, the GNM-GL recommend direct CA in patients with a PTP of > 85%[1,2]. This high-risk cohort made up 7.2% in our study population. With 2.2% of patients with a high PTP and prior NIGT, the application of the ESC-CCS-GL decreased the overall GL-adherence rate by 5.0% (from 25.4% to 20.4%). For Germany this would further increase the number of necessary NIGT by about 25 000 tests per year.

With regard to potential reasons for the GL non-adherent use of CA in Germany, the easy access to 1 078 catheterization laboratories with low waiting times is mentioned in the literature[4,5]. This hypothesis is supported by the health claims data-based analysis of interregional differences in the per capita use of CA in patients with suspected CCS in Germany by Frank-Tewaag et al. who found, that regionally available CA capacities seem to be the trigger of CA utilization and not necessarily the medical need[8]. Furthermore, reimbursement patterns of CA seem to be economically advantageous for health care providers and the mandatory quality assurance program, which does not sanction GL nonadherence, mitigate the interest of health care providers to defer GL-non-adherent patients[4]. In contrast to that, reimbursement of NIGT is less advantageous, e.g. outpatient coronary CT-angiography and stress cardiac magnetic resonance imaging are not refunded by the SHI. To summarize, sufficient NIGT capacities and incentives to adequately provide GL-adherent care seem to be missing in the German health care system. An analysis of potential barriers and facilitators for a GL-adherent care as well as a modelling study addressing the health-economic consequences will be published separately[11].

The content of dissertation project IV has been published in Int J Cardiol Heart Vasc

Limitations

First, the initial patient recruitment target could not be achieved due to several factors: (i) restrictions on patient recruitment during the COVID-19 pandemic, (ii) a cost covering study fee which could not compete with that of industry-sponsored trials, (iii) of 35 addressed study centres 26 did decline participation due to financial reasons but also mentioned the fear of negative consequences as a result of transparency on GL adherence rates towards the participating SHI companies and (iv) due to funding restraints, the recruitment period could not be extended beyond 32 months. As a result, the a priori defined recruitment target of 1 500 patients for the overall study cohort had to be reevaluated, which also led to a decrease in the number of patients obtained for each distinct cohort. However, due to the observational nature of the study, the number of 900 patients overall and 458 patients in this cohort appeared to be sufficient for assessing the degree of GL.

Second, as costs of the diagnostic work-up were gathered on patient-level health claims data as part of the project, only insurees of two participating SHI companies were recruited. However, as these insures represent about 30–35% of all patients in the recruiting centres, the results still can be generalisable, at least for the 90% of Germans being insured in the statutory health system[21].

Third, although the wording of the angina defining questions was derived from the German written GNM-GL, the patient questionnaire and evaluating rules to determine the patients' main complaint was not independently validated[1]. In addition, due to the German written patient informed consent and questionnaire patients with migratory background may be underrepresented. However, its use allowed the estimation of the patients' PTP without a physician bias.

Fourth, the ESC-CCS-GL were introduced during early recruitment and the GNM-GL up to now are not yet adjusted. As outlined, 5.0% of patients switched from GL-adherent to non-adherent, and GL-adherence in general from 25.4% to 20.4%. As the ESC-CCS-GL are endorsed by the German National Cardiac Society they set the new standard of care and replace earlier GL recommendations in Germany[12].

Finally, to take clinical judgement of the referring physicians into account it was decided to include inconclusive findings of the NIGT in the definition for GL-adherent CA. Considering

these 14 cases as nonadherent, overall GL-adherence rate would have even further dropped to 17.1%.

Conclusion

With 20% to 25% of CA in patients transferred with suspected obstructive stable CAD being GL-adherent, this study provides the first prospective evidence on the GL non-adherent use in the majority of CA in Germany in this population. To achieve GL-adherent care, health care resource and refund planning should focus on strengthening the utilization of NIGT. Furthermore, the mandatory quality assurance program should emphasize on both developing methods for reliably assessing the degree of GL-adherence and for enhancing adherence improvement strategies. Finally, while ensuring 24/7 CA access for ACS patients in Germany, the extent of CA capacities in the care of patients with suspected CCS should be carefully evaluated.

Declaration of Competing Interest: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

1. Bundesärztekammer (BÄK), Kassenärztliche Bundesvereinigung (KBV), Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF) 2019. National disease management guidelines for chronic CAD (NVL)—long version, 5th edition. www.khk.versorgungsleitlinien.de (10 February 2023).

2. Knuuti J, Wijns W, Saraste A, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J* 2020;**41**:407–477.

3. Task Force Members; Montalescot G, Sechtem U, Achenbach S, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J* 2013;**34**:2949–3003.

4. Figulla HR, Lauten A, Maier LS, Sechtem U, Silber S, Thiele H. Percutaneous Coronary Intervention in Stable Coronary Heart Disease -Is Less More? *Dtsch Arztebl Int* 2020;**117**:137–144.

5. Institut für Qualitätssicherung und Transparenz im Gesundheitswesen (IQTIG) Bundesqualitätsbericht 2021 - QS-Verfahren Perkutane Koronarintervention (PCI) und Koronarangiographie. Erfassungsjahre 2019 und 2020.

6. Muhlberger V, Ulmer H, Kaltenbach L, Pachinger O. Austrian National CathLab Registry (ANCALAR): cardiac catheterization, coronary angiography (CA), and percutaneous coronary intervention (PCI) in Austria during the year 2013 (Registry Data with Audit including 2014). *Austrian J Cardiol* 2015;**22**:22–26.

7. Möckel M, Searle J, Jeschke E. *Indikation, Prognose und regionale Unterschiede der Herzkatheterversorgung in Deutschland*. 1 edn. In: Versorgungs-Report 2013/2014. editors. Klauber J, Günster C, Gerste B, Robra BP and Schmacke N. Stuttgart: Schattauer; 2014, p. 231–254.

8. Frank-Tewaag J, Bleek J, Gunster C, et al. Regional variation in coronary angiography rates: the association with supply factors and the role of indication: a spatial analysis. *BMC Cardiovasc Disord* 2022;**22**:72.

9. Piedmont S, Swart E, Kenmogne R, Braun-Dullaeus RC, Robra BP. [Left-heart catheterization followed by other invasive procedures: Regional comparisons reveal peculiar differences]. *Z Evid Fortbild Qual Gesundhwes* 2017;127–128:62–71.

10. Baldus S, Werdan K, Levenson B, Kuck KH. Klug entscheiden:... in der Kardiologie. *Dtsch Arztebl International* 2016;**113**:1312–1315.

11. Seleznova Y, Wein B, Muller D, et al. Evaluation of Guideline Adherence for Cardiac Catheterization in Patients With Presumed Obstructive Coronary Artery Disease in Germany (ENLIGHT-KHK) - A Multicentre, Prospective, Observational Study. *Cardiovasc Revasc Med* 2021;**31**:19–25.

12. Möllmann H, Leistner DM, Schulze PC, Sechtem U, Bauersachs J, Kommentar zu den Leitlinien (2019) der ESC zum chronischen Koronarsyndrom, *Kardiologe* 2020;**14**:482–491.

13. Klein J, von dem Knesebeck O, Inequalities in health care utilization among migrants and non-migrants in Germany: a systematic review, *Int J Equity Health* 2018;**17**:160.

14. Deutscher Herzbericht 2020. Frankfurt am Main: Deutsche Herzstiftung.

15. Tchicaya A, Braun M, Lorentz N, Delagardelle C, Beissel J, Wagner D. Social inequality in awareness of cardiovascular risk factors in patients undergoing coronary angiography, *Eur. J Prev Cardiol* 2013;**20**: 872-879.

16. Maurovich-Horvat P, Bosserdt M, Kofoed KF, et al..CT or Invasive Coronary Angiography in Stable Chest Pain, *N Engl J Med* 2022; **386**:1591–1602.

17. Bradley SM, Spertus JA, Kennedy KF et al. Patient selection for diagnostic coronary angiography and hospital-level percutaneous coronary intervention appropriateness: insights from the National Cardiovascular Data Registry, *JAMA* Intern Med 2014;**174**:1630–1639.

18. Al-Hijji MA, Lennon RJ, Gulati R, et al. Safety and Risk of Major Complications With Diagnostic Cardiac Catheterization. *Circ Cardiovasc Interv* 2019;**12**:e007791.

19. Chmiel C, Reich O, Signorell A, Tandjung R, Rosemann T, Senn O. Appropriateness of diagnostic coronary angiography as a measure of cardiac ischemia testing in non-emergency patients - a retrospective cross-sectional analysis. *PloS One* 2015;**10**:e0117172

20. Chmiel C, Reich O, Signorell A, Neuner-Jehle S, Rosemann T, Senn O. Effects of managed care on the proportion of inappropriate elective diagnostic coronary angiographies in non-emergency patients in Switzerland: a retrospective cross-sectional analysis, *BMJ Open* 2018;**8**:e020388.

21. AOK Bundesverband. Zahlen und Fakten 2020. https://www.aokbv.de/imperia/md/aokbv/aok/zahlen/zuf_2020_web.pdf. (10 February 2023).

Chapter 9 Discussion

This cumulative dissertation aimed to evaluate the application of CPG-recommendations in clinical practice based on using invasive CA in chronic CAD in Germany including health-economic effects of CPG-adherence. For this purpose, the extent of adherence to CPG-recommendations was examined. The aim of the dissertation was achieved by conducting four DPs (peer-reviewed publications).

9.1. Main findings from the dissertation projects

9.1.1. Dissertation project I: Scoping review

The scoping review examined the methods used for assessing guideline adherence from the perspective of health care providers for invasive procedures in the care of chronic CAD. The systematic search[1] resulted in twelve studies (311 869 participants) evaluating guideline adherence to European, USA, German and British guidelines. Included studies were similar in the steps of evaluating guideline adherence (i) defining the term, (ii) specifying the study population, (iii) assigning (classes of) recommendations and (iv) quantifying adherence. Thereby, evaluation was mainly based on secondary data. However, included studies varied in the definitions of guideline adherence, i.e. six studies each considered only recommendation class I/grade A/ strong recommendations as adherent or additionally recommendation classes IIa/IIb. In addition, some of the studies reported a priori definitions and allocation rules for assigning recommendation classes. Extent of adherence to CPGs varied from 10% for percutaneous coronary intervention with prior heart team discussion to 98% for coronary artery bypass grafting.[2]

9.1.2. Dissertation project II: Prospective observational study

The prospective observational study ENLIGHT-KHK was conducted to provide evidence on the nature and extent of guideline adherence in patients undergoing a decision-making process for receiving a CA to confirm or exclude an obstructive SCAD in Germany. Overall, 901 patients were recruited in nine centres in North-Rhine Westphalia and Hamburg between January 2019 and August 2021. The study examined the adherence to CPG-recommendations of the GNDMG "Chronic CAD" 2019[3] and the Guidelines of the ESC on "Diagnosis and management of chronic coronary syndromes" 2019[4].[5]

9.1.3. Dissertation project III: Economic evaluation

A cost-effectiveness analysis examined the degree of guideline adherence according to GNDMG 2019[3] and the corresponding clinical and economic outcomes of CA-use in patients with suspected obstructive SCAD. Based on the observed guideline adherence of 25.6% in clinical practice of CA-use, the cost-effectiveness analysis showed that an 'adherent CA-use' would be less expensive and associated with a slightly lower MACE compared with 'real-world CA-use'. Independent on PTP of SCAD, a complete 'adherent CA-use' would lead to a slightly lower rate of MACE (–0.0017) and less cost (€–807) per person compared with 'real-world CA-use'. While cost savings were shown for patients with moderate and low PTP (€901 and €502, respectively), for a high PTP-group, an 'adherent CA-use' results in slightly higher costs (€78) compared with 'real-world CA-use'. Different sensitivity analyses confirmed the results. The evaluation indicates that improving guideline adherence in clinical practice by reducing the amount of CAs in patients with SCAD would lead to cost savings for the German SHI.[6]

9.1.1. Dissertation project IV: Subgroup analysis

As a subgroup analysis in the ENLIGHT-KHK trial[5], it was investigated whether there is a difference in the degree of guideline adherence between the German (GNDMG 2019) and European guideline (ESC 2019) in patients referred for elective CA with suspected obstructive SCAD. Patients (n=458) were in mean 66.6 years old (SD 10.3), 244 (57.3%) of them were male and 206 (48.4%) had a known CAD. Patients presented with anginal symptoms such as typical, atypical or non-anginal chest pain in 152 (35.7%), 176 (41.3%) and 98 (23.0%), respectively. Patients' PTP was in mean 24.2% (11.9 – 36.5%, 95% CI) according to the European and 54.3% (32.4– 76.2%, 95% CI) according to the German guideline. Among 458 patients, 89 (20.9%) underwent a non-invasive image guided test prior to CA. Based on the results on PTP and non-invasive image guided testing received, the CA-use was adherent in 87 patients (20.4%, European guideline[4]) and in 109 patients (25.4%, German guideline[3]).[7]

9.2. Methodological strengths and limitations

9.2.1. Strengths

Overall, the strengths of this dissertation refer to the overall framework for evaluating guideline adherence. As suggested by the UK Medical Research Council, a comprehensive evaluation encompasses various phases and research elements (e.g. evaluation of design and an

underpinning theory)[8]. This dissertation is based on (i) examining the methods of assessing guideline adherence, (ii) developing and conducting a trial, and (iii) analysing the extent of guideline adherence and the corresponding health economic consequences (i.e. clinical and economic outcomes).

The first strength relates to the study design of the ENLIGHT-KHK trial. DP 1 showed that most studies assessing guideline adherence were retrospective and were based on secondary data sources[2]. Since a retrospective design may lead to incomplete, inaccurate and inconsistently measured data[9], a prospective study design[10] generating evidence on guideline adherence was chosen in DP 2[5]. To analyse the use of invasive CA in routine care, both secondary and primary data were defined and collected.

The second strength is the assessment of guideline adherence according to CPG-recommendations (DP 2, DP 3, DP 4). Incorporating the findings of the scoping review (DP 1)[2], the assessment was based on transparent understanding of the construct guideline adherence including objective and standardized a priori defined rules on a patient level. Additionally, the data sources (e.g. patient questionnaire for chest pain symptoms) and variables required (e.g. PTP-group) as well as the analyses conducted were reported transparently (DP 2, DP 3, DP 4).

The third strength is the use of comparative economic evaluation[8] (DP 3[6]). In the cost-effectiveness analysis, alternative courses of action ('adherent CA-use' vs. 'real-world CA-use) were compared in terms of both costs and clinical outcomes (i.e. MACE). This incremental approach provides evidence for potential allocative decisions (i.e. choosing one strategy over another) for the German SHI. Moreover, the use of microsimulation allowed to consider the heterogeneity in patients with suspected obstructive SCAD (i.e. PTP-groups) and examine the varying impact on incremental costs[11].

Fourth, by applying well-established methods which are in line with recommended guidance for modelling[12–14] DP 3 (economic evaluation)[6] provides robust health economic evidence for informing investing/budgeting or allocative decisions on CA-use (due to e.g. model structure, validation efforts and transparent reporting).

Lastly, the GNDMG 2019[3] is a S3-level guideline and represents the highest methodological quality and reliability[15]. Additionally, because the guidelines of the ESC have an impact on the German guidelines, considering the current ESC 2019 guideline[4] (DP 4[7] and sensitivity in DP

3[6]) provides further insights on health economic implications of deviations in guideline adherence. Similar results strengthen the need for improving adherence to CPG-recommendations.

9.2.2. Limitations

The results of this dissertation need to be interpreted with regard to some limitations.

First, the main limitation of DP 3 (economic evaluation) was the level of evidence of the observed adherence to CPG-recommendations in clinical practice (26%)[6]. This outcome was obtained from the ENLIGHT-KHK trial, which had an observational non-interventional study design[5]. Shortcomings inherent to non-comparative effectiveness research (e.g. risk of selection bias[16]) cannot be excluded. However, the ENLIGHT-KHK trial enabled the linkage of primary (i.e. clinical and patient questionnaire-data) and secondary (i.e. claims data from the SHI) data for assessing guideline adherence of CA-use. Moreover, transparent reporting, various model validation efforts, and extensive sensitivity analyses support the findings of the comparative economic evaluation.[6]

Second, a holistic picture of the construct guideline adherence (DP 2, DP 3, DP 4) cannot be ensured. Because neither validated nor standardized instruments for assessing guideline adherence are available[2,6], it was evaluated using a priori (self-) defined evaluating rules, which were formulated according to CPG-recommendations[5]. Although these rules enabled a comprehensive, objective and standardized assessment, they cannot claim to exhaustively present the complex reality of adhering to CPGs[6]. Guideline adherence is influenced by various hindering or facilitating factors such as those on the system-, physician-, guideline-, or the patient level [17,18]. For example, on the system level CA-capacities are higher compared with those of non-invasive testing, which might increase the waiting times for non-invasive testing appointments and favour the referral to CA. In such case, a trade-off between reachability and time might not be captured sufficiently. On the patient level, some contradictions might exist which were not captured but justify the deviation from CPG-recommendation. For example, for some patients a stress-CMR might be contraindicated due to pharmacological stressors and contrast agents or a cCTA due to obesity[6]. However, DP 3 showed that even lower anticipated levels of guideline adherence in clinical practice (e.g. 70%) would still favour improving guideline adherence. Moreover, a transparent reporting of underlying definitions of the

construct guideline adherence (DPs 3 and 4)[6,7] would allow a better understanding of boundaries of its evaluation.

Third, the self-designed patient questionnaire (DP 2, DP 3, DP 4) which was used to determine patients' main complaint (e.g. typical angina) and the evaluating rules (supplementary material to chapter 8, A1-A2) was not validated[7]. However, this allowed to estimate the patients' PTP and the wording of the angina defining questions was obtained from the GNDMG[3].[7]

Finally, the main shortcoming of DP 1 (scoping review) is the lack of quality assessment of the identified methods assessing guideline adherence. This was not conducted due to a lack of a validated instrument[2]. However, as DP 2 aimed to answer the question of which methods were used rather than how accurate these are, this limitation is unlikely to alter the results of this dissertation.

Further specific limitations are reported in the DPs 1 to 4[2,5–7].

9.3. Relation to current state of research

9.3.1. Adherence to CPGs in clinical practice

The findings of this dissertation (DPs 1-4)[2,5–7] indicate that the application of CPG might be not sufficient in clinical practice of chronic CAD. Overall, while a substantial body of evidence exist on guideline development and quality, evidence on the application of CPGs, i.e. adherence to CPGs is limited[19,20]. This corresponds specifically to the findings of DP 1[2] which indicated that assessment of guideline adherence is not well-developed (e.g. due to a lack of standardisation). The still most recent survey by Legido-Quigley et al. (2012) concluded that the extent of the use of clinical guidelines and their evaluation across European countries has not been systematically evaluated[21].

Germany is one of the countries with a well-established system in guideline development and assessment of their quality[19,21]. An example is the NVL-guidelines which inform the content of the nationally structured DMP such as for CAD[22,23]. Physicians who are willing to participate in DMPs sign an obligation to follow the DMP-standards and to document the deviations from adhering to guideline recommendations[24]. For the general CAD population, some evidence on guideline adherence in the DMP-program is available. For example, a pilot study based on German health claims data indicated that DMP-patients received more guideline-adherent

therapy compared with non-DMP-patients[25]. Additionally, the evaluation of DMP-program for CAD showed that 75% of enrolled patients received a guideline-adherent medication therapy with statins[23]. With the exception of DMP-programs, evidence on guideline adherence in CAD is limited. Moreover, evidence from the DMP-programs do not provide information on the chronic CAD or the use of CA.

9.3.2. CA-use in Germany

The amount of CAs in Germany has been subject of the discussion for almost two decades[26–31]. Results of this dissertation provide the first prospective evidence on the extent of the adherence to CPG-recommendations of CA-use in clinical practice in the diagnostic work-up for chronic CAD in Germany. The results in DP 3[6] and DP 4[7] show that guideline adherence of CA-use is suboptimal in patients with suspected chronic CAD and indicate concerns on the amount of CAs (especially of diagnostic CAs).

9.3.3. Cost-effectiveness of guideline-adherent CA-use

The findings of this dissertation (DP 3) suggest that a guideline-adherent use of CA compared with an observed adherence in clinical practice would be cost-saving for the German payer perspective (i.e. SHI). To improve the guideline adherence, decreasing the first-line CAs and increasing the non-invasive testing would be especially required for the moderate PTP-group. Several studies examined the cost-effectiveness of invasive and non-invasive diagnostic testing strategies in patients with symptoms suggestive of chronic CAD (2007-2022)[32–40]. Although the analyses considered the diagnostic accuracy (e.g. false positive or negative results) of the tests, there were important differences related to health economic study design, health care setting and underlying data. These include:

- Stand-alone testing (e.g. CA, stress-CMR, cCTA) or combination of non-invasive and invasive testing (e.g. cCTA and CA),
- Type of CA (e.g. FFR-based[35]),
- Health systems (e.g. UK[34], US[38], Netherlands[36]),
- Effectiveness measures, (e.g. MACE[38], quality adjusted life years[38] correct diagnosis[40]),
- Type of modelling technique (Markov[38], decision-tree[33]) or
- Use of sensitivity analyses (e.g. only deterministic sensitivity analysis[32,33]).

Despite the differences among the studies, the conclusions are in line with the findings of this dissertation (DP 3). Non-invasive image guided testing (i.e. CMR or cCTA) as first-line modality prior to CA is suggested as a cost-effective strategy in patients with a moderate PTP[32,35–39] and CA only in patients with a high PTP[32,33,35,39].

The most recent comparative cost-effectiveness analysis by Nazir et al. (2022)[40] was conducted from the UK payer perspective (i.e. National Health Service). It concluded that a first-line testing with functional imaging (i.e. stress-CMR) is the most cost-effective strategy at low to moderate PTP for a correct diagnosis (willingness to pay €3.500-€28.000) and FFR-based CA might be cost-effective at high PTP. In contrast to findings of this dissertation, the non-FFR based CA was concluded to be not cost-effective. This difference might be due to the reference standard of CA. While the work of Nazir et al. (2022)[40] includes data from recent meta-analyses that used FFR-based CA, in DP 3[6] only 8% of CAs were FFR-based.

Although there is evidence on cost-effectiveness of diagnostic strategies (focusing on diagnostic accuracies) in chronic CAD, to date, DP 3 is the first analysis which examined the costs-effectiveness of adherence to CPGs (complete guideline-adherent vs. observed CA-use) in clinical practice of the diagnostic work-up for chronic CAD.

9.4. Implications for research, policy and practice

To enable CPGs having an impact on clinical practice and patient outcomes, it is not sufficient to develop high-quality CPGs but efforts should also consider dissemination and implementation[19,41] in clinical practice. Dissemination efforts such as access to a wider audience via professional associations and the German AWMF are an important step in translating evidence into clinical practice, however, it is a rather passive dissemination[19,42]. Since awareness of CPGs did not inevitably imply that these are understood or known how to be used[43], more proactive approaches targeting guideline implementation are needed to be prioritised in research, policy and practice.

Guideline implementation interventions consist of various components targeting health professionals, hospital managers, payers, and patients. Intervention may include checklists or electronic decision support systems for health care professionals, self-management tools for patients, evaluation tools for hospital managers, or clinical pathways or multidisciplinary teams for health care provision teams[19,44,45]. However, evidence on effectiveness of implementation

interventions is heterogeneous[42,44–48]. For example, an overarching work of the American College of Cardiology and American Heart Association[46] and a systematic review in cardiovascular diseases[42] concluded that some strategies such as audit, feedback, and educational visits are effective in improving both the processes of care and the clinical outcomes. On the contrary, a Cochrane review in stroke prevention[48] concluded little to no effectiveness of these interventions due low quality of the underlying studies.

Because evidence on effectiveness of guideline implementation strategies is still inconclusive, further research should focus on developing strategies to implementing CPGs and evaluating their effectiveness. Future studies should especially consider contextual factors of guideline implementation in their theoretical basis or framework[8,45]. Overarching[17,44] and cardiology-focused[46,49,50] (systematic) reviews identified barriers and facilitators of guideline implementation that influence the implementation on the (i) system-, (ii) physician-, (iii) patient-, and (iv) the guideline level. Table 2 illustrates potential barriers and facilitators.

Table 2: Potential barriers and facilitators of guideline implementation

Level	**Barriers**	**Facilitators**
System	Lack of time, specialised personnel or health care provision, or financial problems, heavy workload[17,44,49,50]	Consistent leadership, commitment of the team members, multidisciplinary teams[44,46,49]
Physician	Lack of knowledge, skills, self-confidence and -efficacy[17,44,49,50]	Greater knowledge of CPGs, clinical skills and experience using recommendations[49], positive attitudes on CPGs and implementation[17]
Patient	Lack of knowledge about CPGs, sociocultural beliefs[17]	Engagement on recommended interventions[49]
Guideline	Lack of applicability, clarity or credibility[17,44]	Clear, concise, easy to read CPG-recommendations[49]

CPG: Clinical Practice Guideline.

By considering the contextual factors, tailored implementation strategies should be developed and targeted to the specific settings and target groups[44,46]. In particular, for CA-use in patients with chronic CAD in German setting, a qualitative study[18] in the outpatient care suggested that adherence to CPGs is especially hindered by structural aspects at the system level. These aspects include reachability of providers and services (e.g. capacities of cCTAs or stress-CMRs), waiting times, reimbursement through the SHI (e.g. lack of outpatient reimbursement for cCTAs or stress-MRTs), and contract offers. Moreover, implementation strategies that account for interdependencies between barriers and facilitators at various healthcare levels are needed.[18]

To provide conclusive and reliable evidence in the future, development of robust research designs should be strengthened[45,48]. For example, a recent work by Jalloh et al. (2023) in heart failure suggested an evidence-to-care conceptual model that could foster the simultaneous generation of evidence and the long-term implementation of CPGs in clinical practice[51]. Consequently, policy makers such as national funding initiatives[52] should consider implementation aspects in the calls for proposals on topics of CPG-development.

Although the body of evidence on effectiveness of guideline implementation strategies in chronic CAD is to be matured, local guideline implementation efforts in practice should be informed by existing broader effectiveness evidence[42,46], cost-effectiveness evidence (DP 3)[6], and the factors influencing guideline adherence[18]. Because structured implementation strategies indicate to have the most potential to improve guideline adherence[44], an intersectoral health care provision model[50] might improve guideline implementation for the CA-use. This model might include following components:

- Definition of guideline-adherent clinical pathways and patient population (e.g. reduction of diagnostic CAs, increase of non-invasive testing for moderate PTP-group).

- Creating and facilitating a network of providers in inpatient and outpatient care (e.g. general practitioners, cardiologists,), health care payers (i.e. the SHI) and patients associations.

- Promoting knowledge and enhancing skills for health professionals, developing a learning environment with feedback mechanisms (e.g. use of pocket guidelines, key opinion leaders, increasing self-efficacy of physicians).

- Use of electronic decision-support systems[53] to enhance availability of patients' information such as chest pain symptoms or dyspnea, age, gender, PTP, previous testing and results, and decision-making on diagnostic work-up (e.g. by digital patient records, apps, or artificial intelligence technologies).

- Definition of financial incentives and underlying conditions (e.g. non-invasive capacities and referral rules) by using the health economic results[6] and factors influencing guideline adherence[18].

The proposed model would promote the integration of health services and enhance cooperation in cross-sectional and multi-disciplinary health programs, which would correspond with the aims of the German NVL-programs[54].

Because considering diagnostic values of different diagnostic modalities and simultaneous assessment of the risk for CAD might be challenging, the use of artificial intelligence[55,56] as an emerging supplementary technology might foster guideline implementation in the future. However, value and scientific rigor (e.g. validity, reliability and objectivity) of artificial intelligence technologies[57,58] should be ensured prior to their inclusion into clinical practice.

References

1. Tricco AC, Lillie E, Zarin W, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. Ann Intern Med 2018;**169**:467–473.

2. Kentenich H, Müller D, Wein B, Stock S, Seleznova Y. Methods for assessing guideline adherence for invasive procedures in the care of chronic coronary artery disease: a scoping review. *BMJ Open* 2023;**13**:e069832.

3. Bundesärztekammer (BÄK), Kassenärztliche Bundesvereinigung (KBV), Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF) 2019. National disease management guidelines for chronic CAD (NVL)—long version, 5th edition. www.khk.versorgungsleitlinien.de (29 September 2023).

4. Knuuti J, Wijns W, Saraste A, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J* 2020;**41**:407–477.

5. Seleznova Y, Wein B, Muller D, et al. Evaluation of Guideline Adherence for Cardiac Catheterization in Patients With Presumed Obstructive Coronary Artery Disease in Germany (ENLIGHT-KHK) - A Multicentre, Prospective, Observational Study. *Cardiovasc Revasc Med* 2021;**31**:19–25.

6. Seleznova Y, Bruder O, Loeser S, et al. Health economic consequences of optimal vs. observed guideline adherence of coronary angiography in patients with suspected obstructive stable coronary artery in Germany: a microsimulation model. *Eur Heart J Qual Care Clin Outcomes* 2023 Mar 9:qcad015.

7. Wein B, Seleznova Y, Mueller D, et al. Evaluation of the guideline-adherence of coronary angiography in patients with suspected chronic coronary syndrome – Results from the German prospective multicentre ENLIGHT-KHK project. *Int J Cardiol Heart* Vasc 2023;**46**:101203.

8. Skivington K, Matthews L, Simpson SA, et al. A new framework for developing and evaluating complex interventions: update of Medical Research Council guidance. *BMJ* 2021;**374**:n2061.

9. Hulley SB, Cummings SR, Newman TB. Designing Cross-Sectional and Cohort Studies. In: Hulley SB, Cummings SR, Browner WS, Grady GG, Newman TB. *Designing clinical research*. Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins; 2013. p85-96.

10. Vandenbroucke JP, von Elm E, Altman DG, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): Explanation and Elaboration. *PLoS Med* 2007;**4**:e297.

11. Brennan A, Chick SE, Davies R. A taxonomy of model structures for economic evaluation of health technologies. *Health econ* 2006;**15**:1295–1310.

12. Roberts M, Russell LB, Paltiel AD, Chambers M, McEwan P, Krahn M. Conceptualizing a Model: A Report of the ISPOR-SMDM Modeling Good Research Practices Task Force-2. *Value Health* 2012;**15**:804–811.

13. Weinstein MC, O'Brien B, Hornberger J, et al. Principles of Good Practice for Decision Analytic Modeling in Health-Care Evaluation: Report of the ISPOR Task Force on Good Research Practices—Modeling Studies. *Value Health* 2003;**6**:9–17.

14. Caro JJ, Briggs AH, Siebert U, Kuntz KM. Modeling Good Research Practices—Overview: A Report of the ISPOR-SMDM Modeling Good Research Practices Task Force-1. *Value Health* 2012;**15**:796–803.

15. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG) 2023. Was sind Leitlinien? https://www.gesundheitsinformation.de/was-sind-leitlinien.html (29 September 2023).

16. Sterne JAC, Hernán MA, McAleenan A, Reeves BC, Higgins JPT. Chapter 25: Assessing risk of bias in a non-randomized study. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). *Cochrane Handbook for Systematic Reviews of Interventions*. version 6.4 (updated August 2023). Cochrane, 2023. Available from www.training.cochrane.org/handbook.

17. Correa VC, Lugo-Agudelo LH, Aguirre-Acevedo DC, et al. Individual, health system, and contextual barriers and facilitators for the implementation of clinical practice guidelines: a systematic metareview. *Health Res Policy Syst* 2020;**18**:74.

18. Naumann M, Scharfenberg SR, Seleznova Y, et al. Factors influencing adherence to clinical practice guidelines in patients with suspected chronic coronary syndrome: a qualitative interview study in the ambulatory care sector in Germany. *BMC Health Serv Res* 2023;**23**:655.

19. Panteli D, Legido-Quigley H, Reichebner C, et al. Clinical practice guidelines as a quality strategy. In: Busse R, Klazinga N, Panteli D, et al., editors. Improving healthcare quality in Europe: characteristics, effectiveness and implementation of different strategies. Copenhagen (Denmark): European Observatory on Health Systems and Policies; 2019. (Health Policy Series, No. 53.) 9. https://apps.who.int/iris/handle/10665/327356 p233–263.

20. Nothacker M, Muche-Borowski C, Kopp IB. 20 Jahre ärztliche Leitlinien in Deutschland - was haben sie bewirkt? *Z Evid Fortbild Qual Gesundhwes* 2014;**108**:550–559.

21. Legido-Quigley H, Panteli D, Brusamento S, et al. Clinical guidelines in the European Union: Mapping the regulatory basis, development, quality control, implementation and evaluation across member states. *Health Policy* 2012;**107**:146–156.

22. Gemeinsamer Bundesausschuss (GBA) 2023. Disease-Management-Programme. https://www.g-ba.de/themen/disease-management-programme/ (29 September 2023).

23. Kassenärztliche Bundesvereinigung (KBV) 2023. DMP. https://www.kbv.de/html/dmp.php (29 September 2023).

24. Stock, S, Starke, D, Altenhofen, L, Hansen, L. Disease-Management Programs Can Improve Quality of Care for the Chronically Ill, Even in a Weak Primary Care System: A Case Study from Germany. The Commonwealth Fund, November 2011.

25. Schulte T, Mund M, Hofmann L, Pimperl A, Dittmann B, Hildebrandt H. [A pilot study to evaluate the DMP for coronary heart disease - Development of a methodology and first results]. *Z Evid Fortbild Qual Gesundhwes* 2016;110–111:54–59.

26. Dissmann W, Ridder M de. The soft science of German cardiology. *Lancet* 2002;**359**:2027–2029.

27. Figulla HR, Lauten A, Maier LS, Sechtem U, Silber S, Thiele H. Percutaneous Coronary Intervention in Stable Coronary Heart Disease -Is Less More? *Dtsch Arztebl Int* 2020;**117**:137–144.

28. Möckel M, Searle J, Jeschke E. *Indikation, Prognose und regionale Unterschiede der Herzkatheterversorgung in Deutschland*. 1 edn. In: Versorgungs-Report 2013/2014. editors. Klauber J, Günster C, Gerste B, Robra BP and Schmacke N. Stuttgart: Schattauer; 2014, p231–254.

29. Piedmont S, Swart E, Kenmogne R, Braun-Dullaeus RC, Robra BP. [Left-heart catheterization followed by other invasive procedures: Regional comparisons reveal peculiar differences]. *Z Evid Fortbild Qual Gesundhwes* 2017;127–128:62–71.

30. Frank-Tewaag J, Bleek J, Gunster C, et al. Regional variation in coronary angiography rates: the association with supply factors and the role of indication: a spatial analysis. *BMC Cardiovasc Disord* 2022;**22**:72.

31. Deutsche Herzstiftung 2021. *33. Deutscher Herzbericht 2021*. https://herzstiftung.de/system/files/2022-09/DHB21-Herzbericht-2021.pdf (29 September 2023).

32. Dewey M, Hamm B. Cost effectiveness of coronary angiography and calcium scoring using CT and stress MRI for diagnosis of coronary artery disease. *Eur Radiol* 2007;**17**:1301–1309.

33. Boldt J, Leber AW, Bonaventura K, et al. Cost-effectiveness of cardiovascular magnetic resonance and single-photon emission computed tomography for diagnosis of coronary artery disease in Germany. *J Cardiovasc Magn Reson* 2013;**15**:30.

34. Walker S, Girardin F, McKenna C, et al. Cost-effectiveness of cardiovascular magnetic resonance in the diagnosis of coronary heart disease: an economic evaluation using data from the CE-MARC study. *Heart* 2013;**99**:873–881.

35. Moschetti K, Favre D, Pinget C, et al. Comparative cost-effectiveness analyses of cardiovascular magnetic resonance and coronary angiography combined with fractional flow reserve for the diagnosis of coronary artery disease. *J Cardiovasc Magn Reson* 2014;**16**:13.

36. Genders TSS, Petersen SE, Pugliese F, et al. The optimal imaging strategy for patients with stable chest pain: a cost-effectiveness analysis *Ann Intern Med* 2015;**162**:474–484.

37. Lorenzoni V, Bellelli S, Caselli C, et al. Cost-effectiveness analysis of stand-alone or combined non-invasive imaging tests for the diagnosis of stable coronary artery disease: results from the EVINCI study. *Eur J Health Econ* 2019;**20**:1437–1449.

38. Ge Y, Pandya A, Steel K, et al. Cost-Effectiveness Analysis of Stress Cardiovascular Magnetic Resonance Imaging for Stable Chest Pain Syndromes. *JACC Cardiovasc Imaging* 2020;**13**:1505–1517.

39. van Waardhuizen CN, Khanji MY, Genders TSS, et al. Comparative cost-effectiveness of non-invasive imaging tests in patients presenting with chronic stable chest pain with suspected coronary artery disease: a systematic review. *Eur Heart J Qual Care Clin Outcomes* 2016;**2**:245–260.

40. Nazir MS, Rodriguez-Guadarrama Y, Rua T, et al. Cost-effectiveness in diagnosis of stable angina patients: a decision-analytical modelling approach. *Open heart* 2022;**9** e001700.

41. Mickan S, Burls A, Glasziou P. Patterns of 'leakage' in the utilisation of clinical guidelines: a systematic review. *Postgrad Med J* 2011;**87**:670–679.

42. Jeffery RA, To MJ, Hayduk-Costa G, et al. Interventions to improve adherence to cardiovascular disease guidelines: a systematic review. *BMC Fam Pract* 2015;**16**:147.

43. McFarlane E, Chalmers S, Sharma T, Alderson P. DECIDE: survey on awareness of NICE guidelines and their implementation. Berlin; 2012 https://www.decide-collaboration.eu/sites/decide-collaboration.eu/files/uploads/DECIDE_ppt_posterWP3_EMF%20NICE%20survey%20%5BCompatibility%20Mode%5D.pdf.

44. Fischer F, Lange K, Klose K, Greiner W, Kraemer A. Barriers and Strategies in Guideline Implementation—A Scoping Review. *Healthcare (Basel)* 2016;**4**:36.

45. Shanbhag D, Graham ID, Harlos K, et al. Effectiveness of implementation interventions in improving physician adherence to guideline recommendations in heart failure: a systematic review. *BMJ Open* 2018;**8**:e017765.

46. Chan WV, Pearson TA, Bennett GC, et al. ACC/AHA Special Report: Clinical Practice Guideline Implementation Strategies: A Summary of Systematic Reviews by the NHLBI Implementation Science Work Group: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2017;**69**:1076–1092.

47. Kovacs E, Strobl R, Phillips A, Stephan A-J, Müller M, Gensichen J, Grill E. Systematic Review and Meta-analysis of the Effectiveness of Implementation Strategies for Non-communicable Disease Guidelines in Primary Health Care. *J Gen Intern Med* 2018;**33**:1142–1154.

48. Cahill LS, Carey LM, Lannin NA, et al. Implementation interventions to promote the uptake of evidence-based practices in stroke rehabilitation. *Cochrane Database Syst Rev* 2020;**10**:CD012575.

49. Cormican A, Hirani SP, McKeown E. Healthcare professionals' perceived barriers and facilitators of implementing clinical practice guidelines for stroke rehabilitation: A systematic review. *Clin Rehabil* 2023;**37**:701–712.

50. Hoorn CJGM, Crijns HJGM, Dierick-van Daele ATM, Dekker LRC. Review on Factors Influencing Physician Guideline Adherence in Cardiology. *Cardiol Rev* 2019;**27**:80-86.

51. Jalloh MB, Averbuch T, Kulkarni P, et al. Bridging Treatment Implementation Gaps in Patients With Heart Failure: JACC Focus Seminar 2/3. *J Am Coll Cardiol* 2023;**82**:544–558.

52. Förderbekanntmachung Versorgungsforschung – Medizinische Leitlinien (MedLL) - G-BA Innovationsfonds. https://innovationsfonds.g-ba.de/foerderbekanntmachungen/foerderbekanntmachung-versorgungsforschung-medizinische-leitlinien-medll.47 (29 September 2023).

53. Lichtner G, Spies C, Jurth C, et al. Automated Monitoring of Adherence to Evidenced-Based Clinical Guideline Recommendations: Design and Implementation Study. *J Med Internet Res* 2023;**25**:e41177.

54. Ziele und Grundlagen des NVL-Programms 2023. Leitlinien.de. In: Bundesärztekammer (BÄK), Kassenärztliche Bundesvereinigung (KBV), Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF). *Programm für Nationale VersorgungsLeitlinien – Methodenreport*, 5. Auflage. Version 1. 2017 https://www.leitlinien.de/methodik/5-auflage (29 September 2023).

55. Eurlings CGMJ, Bektas S, Sanders-van Wijk S, et al. Use of artificial intelligence to assess the risk of coronary artery disease without additional (non-invasive) testing: validation in a low-risk to intermediate-risk outpatient clinic cohort. *BMJ Open* 2022;**12**:e055170.

56. Zellweger MJ, Tsirkin A, Vasilchenko V, et al. A new non-invasive diagnostic tool in coronary artery disease: artificial intelligence as an essential element of predictive, preventive, and personalized medicine. *EPMA J* 2018;**9**:235–247.

57. Farah L, Davaze-Schneider J, Martin T, Nguyen P, Borget I, Martelli N. Are current clinical studies on artificial intelligence-based medical devices comprehensive enough to support a full health technology assessment? A systematic review. *Artif Intell Med* 2023;**140**:102547.

58. Fasterholdt I, Kjølhede T, Naghavi-Behzad M, Schmidt T, Rautalammi QTS, Hildebrandt MG, Gerdes A, Barkler A, Kidholm K, Rac VE, Rasmussen BSB. Model for ASsessing the value of Artificial Intelligence in medical imaging (MAS-AI). *Int J Technol Assess Health Care* 2022;**38**:e74.

Chapter 10 Conclusion

CPGs are proposed as a strategy for reducing practice variation by enhancing translation of research into clinical practice. For this purpose, CPGs need to be applied in the clinical practice. This cumulative dissertation evaluated the adherence to CPG-recommendations in clinical practice of the invasive CA-use in chronic CAD in Germany by conducting four DPs. A scoping review identified methods used for assessing the guideline adherence of health care providers; a German observational study generated prospective evidence on the extent of adherence to the GNDMG and the ESC guideline; a cost-effectiveness analysis evaluated the clinical and economic consequences of the guideline-adherent CA-use compared with the observed use in clinical practice; and a subgroup analysis examined the differences in guideline adherence between the German and the European CPG-recommendations.

Assessment of guideline adherence is not a well-established and systematically prepared topic. Evidence from the observational study showed that guideline adherence of CA-use is suboptimal in patients with suspected chronic CAD in Germany according to both the German as well the European CPG-recommendations. These findings indicated that the long-standing debate on the amount of the CAs is justified and an overuse of especially diagnostic CAs is likely to be assumed in Germany. From the health economic perspective, improving adherence to CPGs by i) reducing the amount of CAs and ii) strengthening the role of non-invasive image guided testing modalities would result in cost savings and slightly lower MACE for the German SHI.

To improve guideline adherence of diagnostic work-up in chronic CAD, implementation by intersectoral strategies consisting of various components (e.g. education, interdisciplinary networks, and electronic decision-support) might be promising. Especially, these could affect structural barriers and facilitators when translating evidence into clinical practice.

Appendix

Supplementary material to chapter 5 Dissertation project I: scoping review

Supplementary material to chapter 7 Dissertation project III: economic evaluation

Supplementary material to chapter 8 Dissertation project IV: subgroup analysis

Supplementary material to chapter 5

Dissertation project I: scoping review

Supplementary file 1: Electronic Database Searches

Database	Terms
MEDLINE via Pubmed	#1 guideline*[TIAB] #2 guideline adherence[MeSH Terms] #3 adherence [TIAB] #4 Compliance[TIAB] #5 Concordance[TIAB] #6 according[TIAB] #7 non-adherence[TIAB] #8 nonadherence[TIAB] #9 discrepancy[TIAB] #10 appropriate*[TIAB] #11 undertreatment[TIAB] #12 overtreatment[TIAB] #13 underuse[TIAB] #14 under-use[TIAB] #15 overuse[TIAB] #16 over-use #17 misuse[TIAB] #18 investigat*[TIAB] #19 examine[TIAB] #20 identify[TIAB] #21 evaluat*[TIAB] #22 assess*[TIAB] #23 measure*[TIAB] #24 analyz*[TIAB] #25 reliability[TIAB] #26 valid*[TIAB] #27 percutaneous coronary intervention[TIAB] #28 myocardial revascularization[TIAB] #29 coronary revascularization [TIAB] #30 coronary artery bypass graft[TIAB] #31 diagnostic catheterization[TIAB] #32 coronary angiography[TIAB] #33 systematic review[TIAB] #34 meta-analysis[TIAB] #35 (#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10) #36 (#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17) #37 (#17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26) #38 (#27 OR #28 OR #29 OR #30 OR #31 OR #32) #39 (#33 OR #34) #40 (#1 AND #35) #41 (#40 OR #36) #42 (#41 AND #37 AND #38) #43 (#42 NOT #39)
EMBASE via Elsevier	#1 ‘guideline’:ab,ti #2 ‘protocol compliance’/exp

Database	Terms
	#3 ‘adherence’:ab,ti
	#4 ‘Compliance’:ab,ti
	#5 ‘Concordance’:ab,ti
	#6 ‘according’:ab,ti
	#7 ‘non-adherence’:ab,ti
	#8 ‘nonadherence’:ab,ti
	#9 ‘discrepancy’:ab,ti
	#10 ‘appropriate*’:ab,ti
	#11 ‘undertreatment’:ab,ti
	#12 ‘overtreatment’:ab,ti
	#13 ‘underuse’:ab,ti
	#14 ‘under-use’:ab,ti
	#15 ‘overuse’:ab,ti
	#16 ‘over-use’:ab,ti
	#17 ‘misuse’:ab,ti
	#18 ‘investigat*’:ab,ti
	#19 examine:ab,ti
	#20 identify:ab,ti
	#21 ‘evaluat*’:ab,ti
	#22 ‘assess*’:ab,ti
	#23 ‘measure*’:ab,ti
	#24 ‘analyz*’:ab,ti
	#25 ‘reliability’:ab,ti
	#26 ‘valid*’:ab,ti
	#27 ‘percutaneous coronary intervention’:ab,ti
	#28 ‘myocardial revascularization’:ab,ti
	#29 ‘coronary revascularization’:ab,ti
	#30 ‘coronary artery bypass graft’:ab,ti
	#31 ‘diagnostic catheterization’:ab,ti
	#32 ‘coronary angiography’:ab,ti
	#33 ‘systematic review’:ab,ti
	#34 ‘meta-analysis’:ab,ti
	#35 (#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10)
	#36 (#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17)
	#37 (#17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26)
	#38 (#27 OR #28 OR #29 OR #30 OR #31 OR #32)
	#39 (#33 OR #34)
	#40 (#1 AND #35)
	#41 (#40 OR #36)
	#42 (#41 AND #37 AND #38)
	#43 (#42 NOT #39)
	#44 (#43 AND [embase]/lim)
	#45 (#44 NOT ('conference abstract':it OR 'conference paper':ti OR 'conference review':ti OR 'review':it))

Supplementary file 2: Potentially relevant studies and exclusion criteria

No.	Author (Year)	Title	Exclusion criteria
1	Qanitha et al. 2019	Adherence to guideline recommendations for coronary angiography in a poor South-East Asian setting: Impact on short- and medium-term clinical outcomes	Patient adherence
2	Fink et al. 2019	Revascularization Strategies and Survival in Patients With Multivessel Coronary Artery Disease	Guideline adherence no result of the study
3	Ariyaratne et al. 2020	The cost-effectiveness of guideline-driven use of drug-eluting stents: propensity-score matched analysis of a seven-year multicentre experience	No adherence to evidence-based guidelines
4	Anderson et al. 2005	Relationship between procedure indications and outcomes of percutaneous coronary interventions by American College of Cardiology/American Heart Association Task Force Guidelines	No results for patients with chronic CAD
5	Masoudi et al. 2013	Cardiovascular care facts: a report from the national cardiovascular data registry: 2011	Guideline adherence no result of the study
6	Ueki et al. 2019	Validation of High-Risk Features for Stent-Related Ischemic Events as Endorsed by the 2017 DAPT Guidelines	Guideline adherence no result of the study
7	Ziskind et al. 1999	Assessing the appropriateness of coronary revascularization: the University of Maryland Revascularization Appropriateness Score (RAS) and its comparison to RAND expert panel ratings and American College of Cardiology/American Heart Association guidelines with regard to assigned appropriateness rating and ability to predict outcome	No results for patients with chronic CAD
8	Bernstein et al. 2002	Appropriateness of coronary revascularization for patients with chronic stable angina or following an acute myocardial infarction: multinational versus Dutch criteria	No adherence to evidence-based guidelines
9	Dalton et al. 2016	Practice Variation Among Hospitals in Revascularization Therapy and Its Association With Procedure-related Mortality	Guideline adherence no result of the study
10	Powell et al. 2018	Prior Authorization for Elective Diagnostic Catheterization: The Value of Reviewers in Cases with Clinical Ambiguity	No adherence to evidence-based guidelines
11	Sibai et al. 2008	The appropriateness of use of coronary angiography in Lebanon: implications for health policy	No results for patients with chronic CAD
12	De Lima et al. 2010	Treatment of coronary artery disease in hemodialysis patients evaluated for transplant-a registry study	Guideline adherence no result of the study
13	Lenzen et al. 2005	Management and outcome of patients with established coronary artery disease: the Euro Heart Survey on coronary revascularization	Guideline adherence no result of the study
14	Tillmanns et al. 2009	Treatment of chronic CAD--do the guidelines (ESC, AHA) reflect daily practice?	Literature Review
15	Schilling et al. 2003	Assessment of indications in interventional cardiology: appropriateness and necessity of coronary angiography and revascularization	No adherence to evidence-based guidelines

No.	Author (Year)	Title	Exclusion criteria
16	Ormerod et al. 2015	Implementation of NICE clinical guideline 95 on chest pain of recent onset: experience in a district general hospital	Guideline adherence no result of the study
17	Bernardi et al. 2002	The appropriateness of diagnostic angiography in cardiology	No full-text available in English or German
18	Gualano et al. 2010	Temporal trends in the use of drug-eluting stents for approved and off-label indications: a longitudinal analysis of a large multicenter percutaneous coronary intervention registry	Guideline adherence no result of the study
19	Laouri et al. 1997	Underuse of coronary revascularization procedures: application of a clinical method	No adherence to evidence-based guidelines
20	Luciano et al. 2019	Analysis of the appropriate use criteria for coronary angiography in two cardiology services of southern Brazil	No adherence to evidence-based guidelines (AUC)
21	Daly et al. 2005	The initial management of stable angina in Europe, from the Euro Heart Survey: a description of pharmacological management and revascularization strategies initiated within the first month of presentation to a cardiologist in the Euro Heart Survey of Stable Angina	Guideline adherence no result of the study
22	Hatam et al. 2013	Adherence to American Heart Association and American College of Cardiology standard guidelines of angiography in Shiraz, Iran	No results for patients with chronic CAD
23	Bressan et al. 1998	Coronary angiography in two defined populations: Padua and Citadella	No full-text available in English or German
24	Bressan et al. 1993	Coronary angiography in a defined population: a pilot study of the residents of Padua	No full-text available in English or German
25	Daly et al. 2008	Differences in presentation and management of stable angina from East to West in Europe: a comparison between Poland and the UK	Guideline adherence no result of the study
26	Dudley et al. 2002	Age- and sex-related bias in the management of heart disease in a district general hospital	Guideline/Recommendations not clear
27	Casale et al. 2007	"ProvenCareSM"": a provider-driven pay-for-performance program for acute episodic cardiac surgical care	No guideline adherence for invasive procedures in the care of CAD
28	Lee et al. 1990	Feasibility and cost-saving potential of outpatient cardiac catheterization	Guideline adherence no result of the study
29	De Luca et al. 2018	Characteristics, treatment and quality of life of stable coronary artery disease patients with or without angina: Insights from the START study	Guideline adherence no result of the study
30	Yelavarthy et al. 2021	The DISCO study-Does Interventionalists' Sex impact Coronary Outcomes?	No adherence to evidence-based guidelines
31	De Barros E Silva et al. 2018	Improvement in quality indicators using NCDR® registries: First international experience	No adherence to evidence-based guidelines

No.	Author (Year)	Title	Exclusion criteria
32	LaVeist et al. 2003	The cardiac access longitudinal study. A study of access to invasive cardiology among African American and white patients	No results for patients with chronic CAD
33	Cho et al. 2020	Practice Pattern, Diagnostic Yield, and Long-Term Prognostic Impact of Coronary Computed Tomographic Angiography	No adherence to evidence-based guidelines
34	Domingues et al. 2019	Heart Team decision making and long-term outcomes for 1000 consecutive cases of coronary artery disease	Guideline adherence no result of the study
35	Sanei et al. 2017	Evaluation of coronary angioplasty results in patients referring to Isfahan cardiac centers, Iran, and comparing with clinical guidelines	No full-text available in English or German
36	Reid et al. 2014	Is angiography overused for the investigation of suspected coronary disease? A single-centre study	Guideline adherence no result of the study
37	Karthikeyan et al. 2017	Appropriateness-based reimbursement of elective invasive coronary procedures in low- and middle-income countries: Preliminary assessment of feasibility in India	No adherence to evidence-based guidelines (AUC)
38	Berry et al. 2009	ProvenCare: quality improvement model for designing highly reliable care in cardiac surgery	No guideline adherence for invasive procedures in the care of CAD
39	Anderson et al. 2002	A Contemporary Overview of Percutaneous Coronary Interventions	Guideline adherence no result of the study
40	Adamson et al. 2018	Comparison of International Guidelines for Assessment of Suspected Stable Angina: Insights From the PROMISE and SCOT-HEART	Guideline adherence no result of the study
41	Eccleston et al. 2017	Improving Guideline Compliance in Australia With a National Percutaneous Coronary Intervention Outcomes Registry	No guideline adherence for invasive procedures in the care of CAD
42	Din et al. 2017	Variation in practice and concordance with guideline criteria for length of stay after elective percutaneous coronary intervention	No guideline adherence for invasive procedures in the care of CAD
43	Sanchez et al. 2016	Revascularization heart team recommendations as an adjunct to appropriate use criteria for coronary revascularization in patients with complex coronary artery disease	No adherence to evidence-based guidelines (AUC)
44	Greenwood et al. 2016	Effect of care guided by cardiovascular magnetic resonance, myocardial perfusion scintigraphy, or NICE guidelines on subsequent unnecessary angiography rates: The CE-MARC 2 randomized clinical trial	Guideline adherence no result of the study
45	Demarco et al. 2015	Pre-test probability risk scores and their use in contemporary management of patients with chest pain: One year stress echo cohort study	Guideline adherence no result of the study
46	Cubukcu et al. 2015	What's the risk? Assessment of patients with stable chest pain. Echo research and practice	Guideline adherence no result of the study
47	Back et al. 2003	Critical appraisal of cardiac risk stratification before elective vascular surgery	Guideline adherence no result of the study

No.	Author (Year)	Title	Exclusion criteria
48	Kim et al. 2014	Rate of percutaneous coronary intervention for the management of acute coronary syndromes and stable coronary artery disease in the United States (2007 to 2011)	Guideline adherence no result of the study
49	Gandhi et al. 2014	Characteristics and evidence-based management of stable coronary artery disease patients in Canada compared with the rest of the world: insights from the CLARIFY registry	No guideline adherence for invasive procedures in the care of CAD
50	Chan et al. 2013	Patient and hospital characteristics associated with inappropriate percutaneous coronary interventions	No adherence to evidence-based guidelines (AUC)
51	Athauda-Arachchi et al. 2013	Assessing the implications of implementing the NICE guideline 95 for evaluation of stable chest pain of recent onset: A single centre experience	Guideline adherence no result of the study
52	Hannan et al. 2010	Adherence of catheterization laboratory cardiologists to American College of Cardiology/American Heart Association guidelines for percutaneous coronary interventions and coronary artery bypass graft surgery: what happens in actual practice?	No results for patients with chronic CAD
53	Mazzarotto et al. 2009	The use of functional tests and planned coronary angiography after percutaneous coronary revascularization in clinical practice. Results from the AFTER multicenter study	No results for patients with chronic CAD
54	Hemingway et al. 2008	Appropriateness criteria for coronary angiography in angina: Reliability and validity	No adherence to evidence-based guidelines
55	Ugalde et al. 2007	Coronary angiography: indications, results and complications in 5.000 consecutive patients	No full-text available in English or German
56	Darvish et al. 2015	Adherence to practice guidelines for coronary artery bypass graft surgery in Shiraz, Iran	No results for patients with chronic CAD
57	Dworsky et al. 2020	Older veterans undergoing inpatient surgery: What is the compliance with best practice guidelines?	No guideline adherence for invasive procedures in the care of CAD
58	Toth et al. 2021	Revascularization decisions in patients with chronic coronary syndromes: Results of the second International Survey on Interventional Strategy (ISIS-2)	No guideline adherence for invasive procedures in the care of CAD
59	Green et al. 2016	Implementation of a modified version of NICE CG95 on chest pain of recent onset: Experience in a DGH	No guideline adherence for invasive procedures in the care of CAD
60	Komajda et al. 2021	The ESC-EORP Chronic Ischaemic Cardiovascular Disease Long Term (CICD LT) registry	Study Protocol
61	Müller et al. 2001	Referral pattern of the heart catheterization laboratory at the Bern Island University Hospital	No adherence to evidence-based guidelines

No.	Author (Year)	Title	Exclusion criteria
62	Hoffman et al. 2007	Triage of patients with suspected coronary artery disease using multislice computed tomography	No description of the methods for evaluation of guideline adherence
63	Washington et al. 2003	Reliability of clinical guideline development using mail-only versus in-person expert panels	Guideline adherence no result of the study
64	Chmiel et al. 2015	Appropriateness of diagnostic coronary angiography as a measure of cardiac ischemia testing in non-emergency patients - a retrospective cross-sectional analysis	Guideline adherence no result of the study
65	Lurati Buse et al. 2021	Adherence to the European Society of Cardiology/European Society of Anaesthesiology recommendations on preoperative cardiac testing and association with positive results and cardiac events: a cohort study	No results for patients with chronic CAD
66	Orsini et al. 2022	Clinical outcomes of newly diagnosed, stable angina patients managed according to current guidelines. The ARCA (Arca Registry for Chronic Angina) Registry: A prospective, observational, nationwide study	Guideline adherence no result of the study
67	Raposo et al. 2021	Adoption and patterns of use of invasive physiological assessment of coronary artery disease in a large cohort of 40 821 real-world procedures over a 12-year period	Guideline adherence no result of the study

AUC, Appropriate Use Criteria; CAD, Coronary Artery Disease.

Supplementary file 3: Study characteristics

Study	Procedure	Study design and setting	Study period	Study population
Kiselev et al. 2019 [1]	PCI/CABG	Retrospective cross-sectional study RUS, Primary care [2]	Jan 2012 – Dec 2015	1,522 randomly selected patients with stable CAD (stable angina, previous MI, other chronic ischemic heart disease (ICD-10)), CA result and echocardiography including LVEF (exclusion, if ACS within previous 30 days)
Epstein et al. 2003 [3]	PTCA/CABG	Retrospective cohort study US, Care in Medicare Insurance	Jan 1991 – Dec 1992	3,209 randomly selected Medicare beneficiaries aged 65 to 75 with inpatient CA for suspected CAD and diagnosis of chronic stable angina, asymptomatic coronary artery disease, previous MI
O'Connor et al. 2008 [4]	CABG	Retrospective, multicentre cross-sectional study US, cardiac surgery programs in Northern New England	Jan 2004 – Dec 2005	806 patients with CABG and stable angina
Witberg et al. 2014 [5]	PCI, CABG	Prospective single-centre cohort study ISR, medical centre	Jan 2009 – Dec 2010	290 patients referred for PCI or CABG because of LM/3VD without indication for valve surgery or previous CABG/heart transplantation
Leape et al. 2003 [6]	PTCA, CABG	Retrospective cross-sectional study US, Care in Medicare Insurance	Jan 1991 – Dec 1992	819 randomly selected Medicare beneficiaries aged 65 to 75 with CA for suspected CAD and diagnosis of single or multi vessel CAD with class I-V angina and PTCA within 90 days or ischemic heart disease without symptoms, stable angina or post MI and CABG within 90 days
Linder et al. 2018 [7]	PCI	Retrospective cross-sectional analysis GER, Care in statutory health insurance	2008 – 2013	298,574 patients insured by the German statutory health insurance fund with CAD
Marino et al. 2020 [8]	PCI	Retrospective, multicentre cross-sectional pilot study ITA, PCI-performing hospitals	N/A	336 patients with stable CAD

Study	Procedure	Study design and setting	Study period	Study population
Leonardi et al. 2017 [9]	(ad hoc) PCI	Retrospective, multicentre cross-sectional pilot study ITA, PCI-performing hospitals	N/A	148 randomly selected patients with PCI for stable complex CAD and no previous CABG, partly with diabetes mellitus
Yates et al. 2014 [10]	PCI	Prospective, single-centre cohort study with historical control-group UK, hospital (cardiothoracic unit)	Jan – Jun 2011, Jan – Jun 2010	115 patients with stable complex CAD and PCI
Leung et al. 2007 [11]	CA	Prospective single-centre cohort study AUS, Tertiary referral centre (catheterization laboratory)	5 months in 2002	491 consecutive patients with CA for assessment of chest pain
Morgan-Hughes et al. 2021 [12]	CA	Prospective, multicentre cohort study (national audit and service evaluation) UK, CTCA-performing Medical centres	Jan 2018 – Mar 2020	5,293 patients with CTCA for suspected CAD (recent-onset chest pain symptoms); 618 underwent CA
Rubboli et al. 2001 [13]	CA	Retrospective, single-centre cross-sectional study IT, hospital (catheterization laboratory)	Jan 1999 – Dec 1999	266 patients with CA for CAD (stable angina, previous MI)

ACS, acute coronary syndrome; MI, myocardial infarction; CA, coronary angiography; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CTCA, computed tomography coronary angiography; ICD, International Classification of Diseases; LM, left main; LVEF, left ventricular ejection fraction; N/A, not available; PCI, percutaneous coronary intervention; PTCA, percutaneous transluminal angioplasty; 3VD, 3-vessel disease.

Supplementary file 4: Methods and results

Study	Guideline and treatment decision	Data source and collection	Data and variables	Definition of guideline adherence	Quantification and level of measurement	Extent of guideline adherence
Kiselev et al. 2019 [1]	ESC/EACTS 2014 GL on myocardial revascularization Revascularization	Russian registry Retrospective data entry from patient charts by trained study personnel	- Coronary anatomy - Extent of stenosis - LVEF - Clinical history - Symptom status - Therapy	a) Adherence = revascularization if indication b) Non-adherence = indication without revascularization Indication = class I recommendation	Proportion of adherent/non-adherent treatment A binary measure	a) Procedure performed: 81% adherence b) Procedure indicated: 40% adherence
Epstein et al. 2003 [2]	ACC/AHA 1988 GL on PTCA ACC/AHA 1991GL on CABG Revascularization	Medicare data + patient charts Review of coronary angiography report and charts by trained study personnel	- Extent of coronary artery occlusion - Indication for angiography - Severity of angina - Comorbid conditions and risk factors - Medical/surgical history - Medication - Allergies/intolerances - Results of stress tests	a) Non-adherence = no revascularization if indication Indication = recommendation class I b) Non-adherence = revascularization if no indication No indication = class III recommendation	Proportion of non-adherent treatment A binary measure	a) Procedure indicated: ≈ 76% adherence b) Procedure not indicated: ≈ 94% adherence

Study	Guideline and treatment decision	Data source and collection	Data and variables	Definition of guideline adherence	Quantification and level of measurement	Extent of guideline adherence
O'Connor et al. 2008 [3]	ACC/AHA 2004 GL on CABG CABG	American registry Data contribution by centres	- Coronary anatomy - Extent of stenosis - Extent of ischemia - Symptom status - Shock - Prior treatment - Suitability for surgery/PCI - Hemodynamic stability - Cardiac history (e.g. STEMI) - Area of viable myocardium - Results of non-invasive testing	Useful procedure = Recommendation class I Evidence favours procedure = Recommendation class IIa Evidence less well established = Recommendation class IIb Procedure not useful = Recommendation class III Adherence = CABG if recommendation class I or II	Proportion of useful, evidence favours procedure, evidence less well established and not useful procedures + adherent and non-adherent to guidelines A multi-categorical and a binary measure	87% useful (class I) 11% procedure favoured (class IIa) 2% not useful (class III) Overall: 98% adherence
Witberg et al. 2014 [4]	ESC 2010 GL on myocardial revascularization PCI, CABG	Chart review by study personnel Calculation of SS (and cSS) by a study physician not blinded to mode of revascularization using a web-based calculator	- Clinical, laboratory, angiographic characteristics - SS/cSS	Adherence = PCI/CABG according to indication Indication for PCI = recommendation class IIa No indication for PCI/Indication for CABG = recommendation class III for PCI	Proportion of adherent/non-adherent treatment A binary measure	PCI: 78% adherence CABG: 49% adherence

Study	Guideline and treatment decision	Data source and collection	Data and variables	Definition of guideline adherence	Quantification and level of measurement	Extent of guideline adherence
Leape et al. 2003 [5]	ACC/AHA 1988/1993 GL on PTCA ACC/AHA 1991 GL on CABG PTCA, CABG	Medicare data + patient charts Review of coronary angiography report and charts by trained study personnel	Clinical and laboratory data (e.g. symptoms, extent of CAD)	Justified procedure = recommendation class I Uncertain procedure = recommendation class II No indication for procedure = recommendation class III Adherence= procedures rated as justified and uncertain	Proportion of justified, uncertain, not indicated procedures (and adherent and non-adherent to guidelines) A multi-categorical and a binary measure	PTCA, 1988 GL: - 18% justified (class I), - 55% uncertain (class II) - 27% not indicated (class III) - Overall: 73% adherence PTCA, 1993 GL: - 15% justified (class I), - 58 % uncertain (class II) - 27 % not indicated (class III) - Overall: 73% adherence CABG: - 86% justified (class I), - 12% uncertain (class II) - 2% not indicated (class III) - Overall: 98% adherence
Linder et al. 2018 [6]	NVL 2013 on chronic CAD (ESC/EACTS 2014 GL on myocardial revascularization) PCI	Claims data Data record review using ICD-/OPS-/EBM-Codes by study personnel	- ICD-Code (diagnosis, number of lesioned vessels) - EBM/OPS codes for stents implantation	Adherence = no PCI if indication for CABG Indication = recommendation grade A (/Class I recommendation for CABG and class III recommendation for PCI)	Proportion of adherent/non-adherent treatment A binary measure	67% adherence

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Study	Guideline and treatment decision	Data source and collection	Data and variables	Definition of guideline adherence	Quantification and level of measurement	Extent of guideline adherence
Marino et al. 2020 [7]	ESC/EACTS 2018 GL on myocardial revascularization (ACCF/AHA GL 2012 on stable ischemic heart disease) PCI, Ad hoc PCI	Patient charts Review of chart and coronary angiogram and determination of PTP by study personnel Definition of SS and SYNTAX Revascularization Index, coronary anatomy and presence of 'borderline' stenosis by study personnel	- SS - Coronary anatomy - Significance of stenoses	a) Adherence = PCI if strong recommendation for PCI or similar recommendation for PCI/CABG Strong recommendation = Class I recommendation for PCI and class IIb for CABG Similar recommendation = Class I recommendation for PCI and class I for CABG, class IIa recommendation for PCI and class I/II for CABG b) Non-adherence = ad hoc PCI if indication for heart team discussion Indication = recommendation class I for CABG	Proportion of adherent/non-adherent treatment A binary measure	a) PCI: 91% adherence b) Ad hoc PCI: 17% adherence

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Study	Guideline and treatment decision	Data source and collection	Data and variables	Definition of guideline adherence	Quantification and level of measurement	Extent of guideline adherence
Leonardi et al. 2017 [8]	ESC 2013 GL on stable CAD ESC/EACTS 2014 GL on myocardial revascularization Ad hoc PCI, PCI with heart team discussion	Review of chart and coronary angiogram and determination of PTP by study personnel Definition of SS, coronary anatomy and presence of 'borderline' stenosis by study personnel	- Coronary anatomy - Significance of stenoses - SS - Evidence of heart team discussion	a) Adherence = heart team discussion if indication b) Non-adherence = ad hoc PCI if indication for heart team discussion Indication = recommendation class I for heart team, recommendation class I for CABG	Proportion of adherent/non-adherent treatment A binary measure	a) Heart team discussion: 11% adherence b) Ad hoc PCI: 20% adherence
Yates et al. 2014 [9]	ESC/EACTS 2010 GL on myocardial revascularization PCI with heart team discussion	British registry, records on heart team discussion Prospective data collection during PCI in registry by care providers Review of database of all patients discussed by the heart team by study personnel, minutes recorded at each meeting	- Coronary anatomy - Significance of stenoses - Diagnosis - Management plan - Reasons for deviation from expected practice	Adherence = heart team discussion before revascularization if indication Indication = recommendation class I	Proportion of adherent/non-adherent treatment A binary measure	2010: 10% adherence 2011: 19% adherence

Study	Guideline and treatment decision	Data source and collection	Data and variables	Definition of guideline adherence	Quantification and level of measurement	Extent of guideline adherence
Morgan-Hughes et al. 2021 [10]	NICE CG95 (2016) CA	Prospective data collection at participating centres in patient records and picture archiving/communication systems and anonymized collation at audit centre Definition of CTCA as diagnostic or not by reporting cardiologist/radiologist using own criteria	- Demographic information - CTCA results - Diagnostic tests - Revascularization	Non-adherence = Overuse of CA Surrogate: Overuse of CA = CA without strong recommendation and revascularization	Proportion of adherent/non-adherent (overuse of CA) treatment A binary measure	52% adherence
Leung et al. 2007 [11]	ACC/AHA 1999 GL on CA CA	N/A Prospective data recording by study personnel Classification (visual) of chest pain and estimation of the degree of coronary stenosis by experienced study personnel	- Clinical history - Coronary risk factors (e.g. diabetes mellitus, smoking) - Symptoms - Results of electrocardiograms and laboratory tests - Extent of stenosis - Prior treatment	Adherence = CA if recommendation class I or II (Non-adherence = CA if recommendation class III or no recommendation class I or II)	Proportion of adherent/non-adherent treatment A binary measure	53% adherence
Rubboli et al. 2001 [12]	ACC/AHA 1999 GL for CA	Chart review by study personnel	- Clinical diagnosis (indication) - Comorbidities - Cardiovascular risk factors	Useful procedure = recommendation class I Evidence favours procedure = recommendation class IIa	Proportion of useful, evidence favours procedure, evidence less well established and not useful	Approx. 71% useful Approx. 8% favoured (class IIa) 21% less established (class IIb) Overall:

Study	Guideline and treatment decision	Data source and collection	Data and variables	Definition of guideline adherence	Quantification and level of measurement	Extent of guideline adherence
	CA	Charts filled out by catheterization cardiologist	- Laboratory test results - Instrumental examination results - Ongoing treatment	Evidence less well established = recommendation class IIb Non-useful procedure = recommendation class III Adherence = CA if recommendation class I (useful) or IIa (evidence favours procedure) Uncertain = CA if recommendation class IIb (evidence less well established) Non-adherence = CA if recommendation class III (not useful)	procedures + adherent, uncertain and non-adherent procedures A multi-categorical measure	79% adherent (class I /IIa) 21% uncertain (class IIb) 0% non-adherent (class III)

ACC, American College of Cardiology; ACCF, American College of Cardiology Foundation; AHA, American Heart Association; CA, coronary angiography; CABG, coronary artery bypass grafting; CAD, coronary artery disease; cSS, clinical syntax score; CTCA, computed tomography CA; DM, diabetes mellitus; EBM, common assessment scale; ESC, European Society of Cardiology; EACTS, European Association for Cardio-Thoracic Surgery; GL, guideline; ICD, International Classification of Diseases; (LV)EF; (Left Ventricular) ejection fraction; LVF, Left Ventricular Function; (N)STEMI, (non-)ST-segment Elevation Myocardial Infarction; NVL, National disease management guideline; OPS, operation and procedure codes; PCI, percutaneous coronary intervention; PTCA, percutaneous transluminal coronary angioplasty; PTP, pre-test probability; SS, syntax score.

References

1. Kiselev AR, Korotin AS, Posnenkova OM, et al. Discrepancy between the European clinical guidelines and myocardial revascularization in patients with stable coronary artery disease in Russia. *Int J Qual Health Care* 2019 May 1;**31**:269-275.
2. Epstein AM, Weissman JS, Schneider EC, et al. Race and gender disparities in rates of cardiac revascularization: do they reflect appropriate use of procedures or problems in quality of care? *Med Care* 2003 Nov;**41**:1240-1255.
3. O'Connor GT, Olmstead EM, Nugent WC, et al. Appropriateness of Coronary Artery Bypass Graft Surgery Performed in Northern New England. *J Am Coll Cardiol* 2008;**51**:2323-2328.
4. Witberg G, Lavi I, Gonen O, et al. Long-term outcomes of patients with complex coronary artery disease according to agreement between the SYNTAX score and revascularization procedure in contemporary practice. *Coron Artery Dis* 2014 Jun;**25**:296-303.
5. Leape LL, Weissman JS, Schneider EC, et al. Adherence to practice guidelines: The role of specialty society guidelines. *Am Heart J* 2003;**145**:19-26.
6. Linder R, Zeidler J, Verheyen F, et al. Guidelines versus reality: is coronary stent application in three-vessel disease standard or the exception? *Eur J Health Econ* 2018 Jul;**19**:821-830.
7. Marino M, Leonardi S, Crimi G, et al. Lack of implementation of guidelines recommendations for coronary revascularization in stable patients with complex disease is associated with high rates of incomplete revascularization: Analysis from the Apache study. *Heart Vessels* 2020 Jan;**35**:30-37.
8. Leonardi S, Marino M, Crimi G, et al. APpropriAteness of percutaneous Coronary interventions in patients with ischaemic HEart disease in Italy: the APACHE pilot study. *BMJ Open* 2017 Sep 5;**7**:e016909.
9. Yates MT, Soppa GK, Valencia O, et al. Impact of European Society of Cardiology and European Association for Cardiothoracic Surgery Guidelines on Myocardial Revascularization on the activity of percutaneous coronary intervention and coronary artery bypass graft surgery for stable coronary artery disease. *J Thorac Cardiovasc Surg* 2014 Feb;**147**:606-610.
10. Leung DY, Hallani H, Lo ST, et al. How compliant are we with guidelines for coronary angiography in clinical practice? *Intern Med J* 2007;**37**:699-704.
11. Morgan-Hughes G, Williams MC, Loudon M, et al. Downstream testing after CT coronary angiography: time for a rethink? *Open heart* 2021 Feb;**8**(1).
12. Rubboli A, La Vecchia L, Casella G, et al. Appropriateness of the use of coronary angiography in a population of patients with ischemic heart disease. *Ital Heart J* 2001 Sep;**2**:696-701.

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Supplementary material to chapter 7

Dissertation project III: economic evaluation

Checklist S1: Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022)

Topic	No.	Item	Location where item is reported
Title			
	1	Identify the study as an economic evaluation and specify the interventions being compared.	Title page
Abstract			
	2	Provide a structured summary that highlights context, key methods, results, and alternative analyses.	Abstract
Introduction			
Background and objectives	3	Give the context for the study, the study question, and its practical relevance for decision making in policy or practice.	Introduction
Methods			
Health economic analysis plan	4	Indicate whether a health economic analysis plan was developed and where available.	Section "Methods", first paragraph
Study population	5	Describe characteristics of the study population (such as age range, demographics, socioeconomic, or clinical characteristics).	Subsection "Patient population and comparators" first paragraph; Supplementary material: Table S1
Setting and location	6	Provide relevant contextual information that may influence findings.	Section "Methods", first and second paragraph
Comparators	7	Describe the interventions or strategies being compared and why chosen.	Subsection "Patient population and comparators" second paragraph
Perspective	8	State the perspective(s) adopted by the study and why chosen.	Section "Methods", second paragraph
Time horizon	9	State the time horizon for the study and why appropriate.	Section "Methods", second paragraph
Discount rate	10	Report the discount rate(s) and reason chosen.	Subsection "Resource utilization and costs", last paragraph
Selection of outcomes	11	Describe what outcomes were used as the measure(s) of benefit(s) and harm(s).	Section "Methods", second paragraph
Measurement of outcomes	12	Describe how outcomes used to capture benefit(s) and harm(s) were measured.	Section "Methods", first paragraph; Subsection "Model inputs" first paragraph and subsections "Guideline adherence" and "Clinical data"
Valuation of outcomes	13	Describe the population and methods used to measure and value outcomes.	Not Applicable
Measurement and valuation of resources and costs	14	Describe how costs were valued.	Subsection "Resource utilization and costs"

Currency, price date, and conversion	15	Report the dates of the estimated resource quantities and unit costs, plus the currency and year of conversion.	Subsection "Resource utilization and costs" last paragraph
Rationale and description of model	16	If modelling is used, describe in detail and why used. Report if the model is publicly available and where it can be accessed.	Subsection "Model description"
Analytics and assumptions	17	Describe any methods for analysing or statistically transforming data, any extrapolation methods, and approaches for validating any model used.	Subsections "Guideline adherence", "Clinical data", "Resource utilization and costs"; "Model validation"
Characterising heterogeneity	18	Describe any methods used for estimating how the results of the study vary for subgroups.	"Clinical data" last paragraph
Characterising distributional effects	19	Describe how impacts are distributed across different individuals or adjustments made to reflect priority populations.	Not applicable
Characterising uncertainty	20	Describe methods to characterise any sources of uncertainty in the analysis.	Subsection "Sensitivity analyses"
Approach to engagement with patients and others affected by the study	21	Describe any approaches to engage patients or service recipients, the general public, communities, or stakeholders (such as clinicians or payers) in the design of the study.	Subsection "Model validation"
Results			
Study parameters	22	Report all analytic inputs (such as values, ranges, references) including uncertainty or distributional assumptions.	Tables 1-3, Supplementary material: Text S4 and Table S5
Summary of main results	23	Report the mean values for the main categories of costs and outcomes of interest and summarise them in the most appropriate overall measure.	Subsection "Base-case analysis"
Effect of uncertainty	24	Describe how uncertainty about analytic judgments, inputs, or projections affect findings. Report the effect of choice of discount rate and time horizon, if applicable.	Subsection "Sensitivity analyses"
Effect of engagement with patients and others affected by the study	25	Report on any difference patient/service recipient, general public, community, or stakeholder involvement made to the approach or findings of the study	Supplementary material: Questionnaire S8
Discussion			
Study findings, limitations, generalisability, and current knowledge	26	Report key findings, limitations, ethical or equity considerations not captured, and how these could affect patients, policy, or practice.	Section Discussion
Other relevant information			
Source of funding	27	Describe how the study was funded and any role of the funder in the identification, design, conduct, and reporting of the analysis	Subsection "Funding"
Conflicts of interest	28	Report authors conflicts of interest according to journal or International Committee of Medical Journal Editors requirements.	Subsection "Conflicts of Interest"

From: Husereau D, Drummond M, Augustovski F, et al. Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) Explanation and Elaboration: A Report of the ISPOR CHEERS II Good Practices Task Force. Value Health 2022;25. doi:10.1016/j.jval.2021.10.008

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Table S2: Baseline characteristics of the patient population of the ENLIGHT-KHK trial

	Overall population
N	**901**
Demographics	
Age (years)	64,9 ± 11,8
Gender, male	524 (58.2)
BMI in kg/m²	29,5 (5.9)
Risk profile	
Arterial hypertension	726 (80.9)[a]
Hypercholesterolaemia /dyslipidaemia	489 (55.1)[b]
Diabetes mellitus	269 (30.1)[c]
Family history of CAD	304 (39.3)[d]
Known CAD	388 (43.2)[e]
Prior MI	162 (18.1)[f]
Type of chest pain (patient reported)	
Typical angina pectoris	271 (31.7) [g]
Atypical angina pectoris	339 (39.6) [g]
Non-anginal pain	245 (28.7) [g]
Pre-test probability	
Low (<15%)	34 (4.0)[g]
Intermediate (15-85%)	773 (90.4)[g]
High (>85%)	48 (5.6)[g]

Values are n (%) or mean ± SD. [a] n = 897, [b] n = 888, [c] n=894, [d] n = 773, [e] n = 898, [f] n = 897, [g] n = 855

BMI, body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention.

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Table S3: Summary of recommendations for the diagnostic work-up of the German National Disease Management Guideline on Stable Coronary Artery Disease and rationale for evaluating guideline adherence

Pre-test Probability	**Guideline recommendation**	**Non-Invasive Image Guided Testing[a]**	**Guideline-Adherence of Coronary Angiography**
Low <15%	No further testing	Not done or non-pathological	No
		Pathological or inconclusive results	Yes
Intermediate 15-85%	Non-invasive image-guided testing	Not done or non-pathological	No
		Pathological or inconclusive results	Yes
High >85%	Direct coronary angiography	Irrespective of non-invasive testing	Yes

[a] Stress-echocardiography, coronary computed tomography angiography, myocardial perfusion scintigraphy, or cardiac stress magnetic resonance imaging.

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Table S4: Data underlying the clinical inputs and resource utilization parameters of the model

	Overall population
N	**901**
Performed procedures	n (%)
CA	695 (77.1)
With FFR	55 (7.9)
Result	
One vessel disease	123 (17.7)
Two vessel disease	122 (17.6)
Three vessel disease	199 (28.6)
Coronary sclerosis without >50% stenosis	77 (11.1)
CAD rule-out	149 (21.4)
Other (e.g. hypertensive heart disease)	25 (3.6)
Therapy decision	
PCI	248 (35.7)
CABG	25 (3.6)
No specific therapy	137 (19.7)
Medical therapy	248 (41)
cCTA	105 (11.7)
positive	43 (41.3)[a]
negative	38 (36.5)[a]
unclear	23 (22.1)[a]
Stress-echo	19 (2.1)
positive	4 (21.1)
negative	10 (52.6)
unclear	5 (26.3)
Stress-CMR	140 (15.5)
positive	32 (22.9)
negative	101 (72.1)
unclear	7 (5.0)
MPS	66 (7.3)
positive	38 (57.6) [b]
negative	11 (16.7) [b]
unclear	14 (21.2)[b]
eECG	185 (20.5)
positive	70 (37.8)[c]
negative	32 (17.3)[c]
unclear	68 (36.76)[c]

[a] n = 104, [b] n = 63, [c] n=170.

CA, coronary angiography; CABG, coronary artery bypass grafting; CAD, coronary artery disease; cCTA, coronary computed tomography angiography; CMR, cardiac magnetic resonance; eECG, exercise electrocardiogram; FFR, fractional flow reserve; MPS, myocardial perfusion scintigraphy; PCI, percutaneous coronary intervention

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Text S5: Details on MACE

From 695 patients who underwent a diagnostic or therapeutic CA, six (0.9%) experienced a MACE (myocardial infarction = 4, stroke/TIA = 2 and none all-cause death). Three patients (0.7%) MACE were associated with diagnostic CAs (n = 422) and three (1.1%) with therapeutic CAs (n = 273), respectively. On average, patients had a moderate PTP of 49.8% (SD 25.1)).

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Table S6: Sensitivity analysis examining the impact of different degree of guideline adherence (improved adherence)

Guideline adherence in the 'adherent CA-use' arm	Reduction of non-adherent CAs (observed guideline adherence of 26%)	Probability for CA with prior NIT for moderate PTP (15-85%)
100%	0.74	0.295
90%	0.64	0.342
80%	0.54	0.386
70%	0.44	0.427

CA, coronary angiography; NIT, non-invasive testing; PTP, pre-test probability.

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Table S7: Sensitivity analysis examining the impact of guideline adherence according to the 2019 ESC guidelines

	Value[a]	**Source**
'Real-world CA-use'	Rate (%)	
Overall guideline adherence (n = 656)	140 (21.3)	Patients' records from nine participating hospitals
First-line CA[b] (n = 421)	0 (0)	
Low PTP (<15%)	0/10 (0)	
Moderate PTP (15-85%)	0/387 (0)	
High PTP (>85%)	0/24 (0)	
CA with prior NIT (n = 235)	140 (0.60)	
Low PTP (<15%)	3/4 (0.75)	
Moderate PTP (15-85%)	127/211 (0.6)	
High PTP (>85%)	10/20 (0.5)	
'Adherent CA-use'		
(100% guideline adherence)	Probability (95 % CI)	
First-line CA[b]		
ppt <15% (0)	0	
ppt 15-85% (0)	0	
ppt >85% (0)	0	
CA with prior NIT		
ppt <15% (0.013)	0.179 [0.018, 0.313]	
ppt 15-85% (0.540)	0.308 [0.273, 0.341]	
ppt >85% (0.042)	0.355 [0.213, 0.471]	

CA, coronary angiography; CI, confidence interval; NIT, non-invasive testing; PTP, pre-test probability.

[a] All other clinical and cost data remain the same as in Table 2 and Table 3.

[b]First-Line CA means CA without preceding NIT.

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Questionnaire S8: Model validation by using the Assessment of the Validation Status of Health-Economic decision models (AdViSHE)

Part A: Validation of the conceptual model (2 questions)

A1/Face validity testing (conceptual model): Have experts been asked to judge the appropriateness of the conceptual model?
- Prof. Dr. med. Oliver Bruder (cardiologist), Dr. med. Bastian Wein (cardiologist) and PD Dr. med. Robert Schueler (cardiologist). Clinical experts have judged whether the underlying clinical process is appropriately represented by the model. - Dr. med. Simon Loeser (AOK RHeinland Hamburg, Head of Inpatient Division, Statutory Health Insurance (SHI)). The expert for German statutory health care verified the appropriateness of the model for evaluation from the perspective of the German SHI (i.e., reimbursement rules, costs).
A2/ Cross validation testing (conceptual model): Has this model been compared to other conceptual models found in the literature or clinical textbooks?
- The model structure has been compared to models analysing similar research questions (Moschetti 2022, Nazir 2022).

Part B: Input data validation (2 questions)

B1/ Face validity testing (input data): Have experts been asked to judge the appropriateness of the input data?
- Dr. med. Bastian Wein (cardiologist), Prof. Dr. med. Oliver Bruder (cardiologist) and Dr. med. Simon Loeser (AOK RHeinland Hamburg, Head of Inpatient Division, Statutory Health Insurance (SHI)) verified the clinical input parameters and data on resource utilization and costs. - A perfect guideline adherence (i.e., 100%) may not be achievable in the clinical practice and the potential for reductions of coronary angiography (CA) might be overestimated to some extent, therefore we tested for different degrees of guideline adherence (e.g. 70-90%) by means of structural sensitivity analyses. - The average costs for CA might be overestimated to some extent, however due to a high number of inpatient CAs (77%), these costs were deemed to be appropriate for ENLIGHT-KHK population. This should be taken into account, if generalizing to other settings, where a higher number of CAs in an outpatient setting are performed.
B2/ Model fit testing: When input parameters are based on regression models, have statistical tests been performed?
- Not applicable, since no regression models have been constructed.

Part C: Validation of the computerized model (4 questions)

C1/ External review: Has the computerized model been examined by modelling experts?
- The computerized model has been examined by two modelers (Yana Seleznova and Dirk Müller) included in the analysis.
C2/ Extreme value testing: Has the model ben run for specific, extreme sets of parameter values in order to detect any coding errors.
- Extreme values were applied for clinical and economic parameters. For example, the parameter CA-associated major adverse cardiovascular events (MACE) were set to be zero and the differences in effects resulted in zero.
C3/ Testing of traces: Have patients been tracked through the model to determine whether its logic is correct?

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C4/ Unit testing: have individual sub-modules of the computerized model been tested?
- Yes. For example, the pathway of first-line CA was run only.

Part D: Operational validation (2 questions)

D1/ Face validity testing (model outcomes): have experts been asked to judge the appropriateness of the model outcomes?
- Dr. med. Bastian Wein (cardiologist), Prof. Dr. med. Oliver Bruder (cardiologist) and Dr. med. Simon Loeser (Head of Inpatient Division, AOK RHeinland Hamburg, Statutory Health Insurance (SHI)) verified the clinical input parameters and data on resource utilization and costs. - the marginal increment effect between the perfect guideline-adherent practice and observed clinical practice (-0.0017) confirms the ex-ante assumptions on the effect measure because CA is considered to be a safe and well-established procedure in cardiology. - the estimated total costs of the real-world adherence pathway (€2205,84) were reasonable because it is similar to the costs of CA (F49G, €2,454) the most reimbursed code for a CA in Germany.
D2/ Cross validation testing (model outcomes): Have the model outcomes been compared to the outcomes of other models that address similar problems?
- The model results were compared to models analysing similar research questions.
D3/ Validation against outcomes using alternative input data: Have the model outcomes been compared to the outcomes obtained when using alternative input data?
- No changes on overall results. These input data were compared with alternative sources: - CA-associated MACE: Within a Cochrane review (Kolkailah 2018), only three included studies (Achenbach 2008, Brueck 2009, Lange 2006) considered the German setting. Studies reported a low rate of complications (e.g. 0,2% for cerebrovascular accidents Brueck 2009), however, in the studies either the patients were older than the ENLIGHT-KHK population (Achenbach 2008) or they included patients with an unstable coronary syndrome. Consequently, we concluded this is reasonable to take the incidence of CA-associated MACE from ENLIGHT-KHK. - Because of a low incidence of MACE and the corresponding documented DRGs, we estimated the MACE-costs based on national public sources (Reimbursement 2022) (€6,569) which were comparable with our estimate (€ 6,429) (i.e., within the bootstrapped 95% confidence interval). - Estimated costs of diagnostic CA (€2,431) and PCI (€4,128) were compared with costs (F49G: diagnostic CA €2545; F56B: PCI 4,255) which are charged to the SHI available from publicly sources (Reimbursement 2022).
D4/ Validation against empirical data: Have the model outcomes been compared to empirical data?
- See D3.

Part E: Other validation techniques (1 question)

E1/ Other validation techniques: Have other validation techniques been performed?
- Double-check of programming and run all analyses several times.

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Figure S9: Results of the probabilistic sensitivity analysis showing the distributions of incremental costs and effects for ‘adherent CA-use’ vs. ‘real-world CA-use’

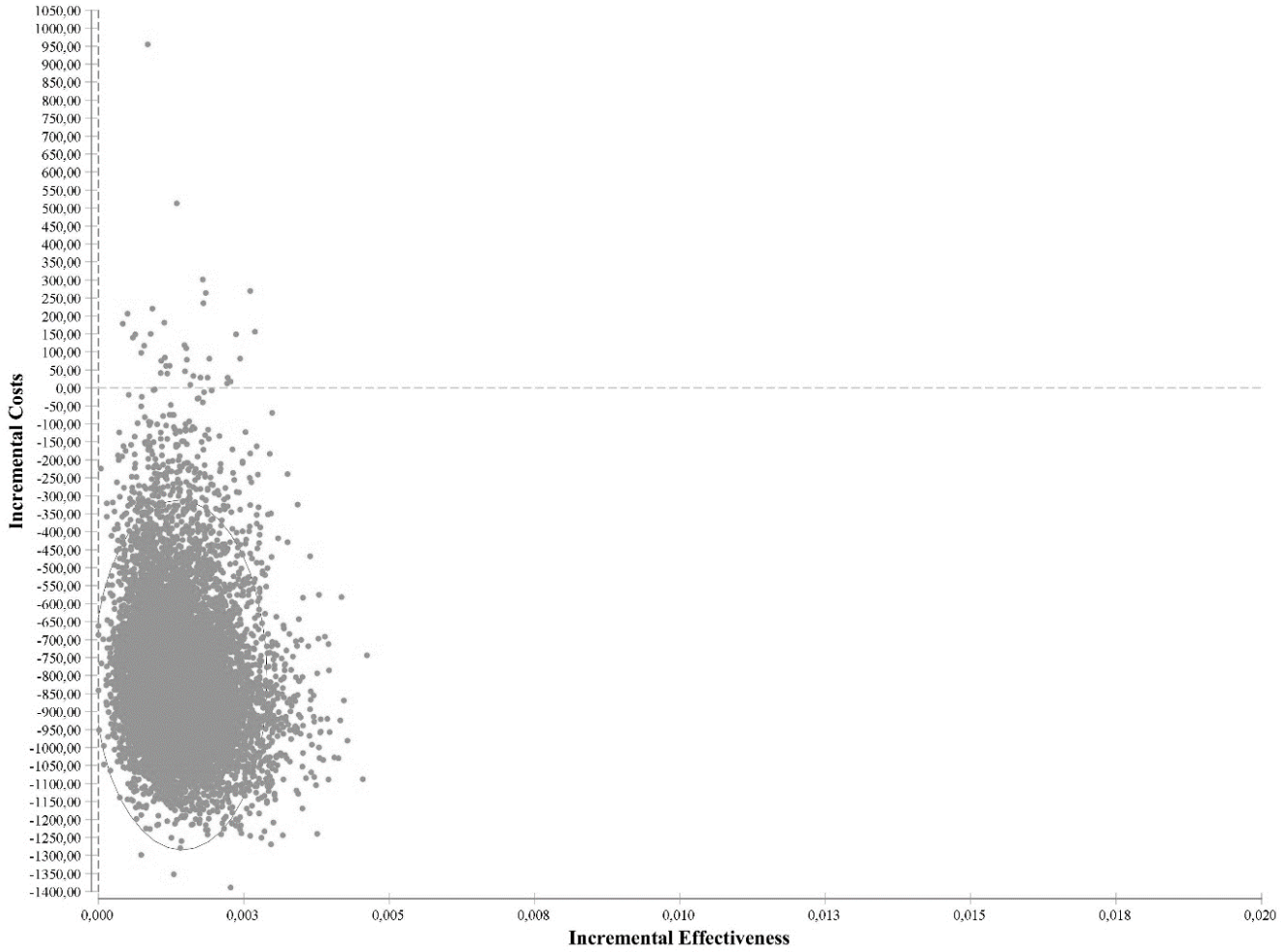

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Table S10: Results of sensitivity analyses analyzing the impact of varying degree of perfect adherence

Indication process	**Costs (€) per person and process**	**Cost difference (€) per person and process**	**MACE-event per person and process**	**Effect difference (averted MACE-event per person)**	**ICER (€ per averted MACE-event)**
Basecase: overall population					
'Adherent CA-use' (assumed)	1398	-807	0.0019	-0.0017	dominates[a]
'Real-world CA-use' (observed)	2206		0.0036		
Analysis 1: Guideline adherence 90%					
'Adherent CA-use' (assumed)	1527	-679	0.0021	-0.0015	dominates[a]
'Real-world CA-use' (observed)	2206		0.0036		
Analysis 2: Guideline adherence 80%					
'Adherent CA-use' (assumed)	1651	-555	0.0023	-0.0013	dominates[a]
'Real-world CA-use' (observed)	2206		0.0036		
Analysis 3: Guideline adherence 70%					
'Adherent CA-use' (assumed)	1766	-440	0.0025	-0.0011	dominates[a]
'Real-world CA-use' (observed)	2206		0.0036		

ICER, incremental cost-effectiveness ratio; MACE, major adverse cardiovascular event.

[a] 'Adherent CA-use' is less costly and more effective in averting MACE compared with 'Real-world CA-use'.

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Table S11: Results of sensitivity analyses examining the impact of guideline adherence according to the 2019 ESC

		Costs (€) per person and process	**Cost difference (€) per person and process**	**MACE per person and process**	**Effect difference (averted MACE per person)**	**ICER (€ per averted MACE)**
Overall population						
'Adherent CA-use' (assumed)		1341	-866	0.0018	-0.0018	dominates[a]
'Real-world CA-use' (observed)		2206		0.0036		
PTP <15%						
'Adherent CA-use' (assumed)		401	-497	0	0	undefined
'Real-world CA-use' (observed)		898		0		
PTP 15%-85%						
'Adherent CA-use' (assumed)		1295	-901	0.0017	-0.0018	dominates[a]
'Real-world CA-use' (observed)		2196		0.0035		
PTP >85%						
'Adherent CA-use' (assumed)		1568	-837	0.0044	0	undefined
'Real-world CA-use' (observed)		2405		0.0044		

ICER, incremental cost-effectiveness ratio; MACE, major adverse cardiovascular event; PTP, pre-test probability.

a 'Adherent CA-use' is less costly and more effective in averting MACE compared with 'real-world CA-use'.

Supplementary material to chapter 8

Dissertation project IV: subgroup-analysis

A.1. Patient questionnaire A.1.1. English version (Translation)

Dear Study Participant,

with this questionnaire we would like to find out, which complaints have led you to us and how you assess them. To be able to compare your answers with those of other participants, we are addressing you with a standardized questionnaire with mostly predefined answer options.

Please tick the appropriate box or boxes:

1. Symptomatic complaints

   Here we would like to ask you about your main complaints from a cardiological point of view.

   1.1. What is your main complaint that you came to us about?

   Chest discomfort □

   Discomfort outside the chest area □

   Shortness of breath □

   Reduced exercise capacity □

   Palpitations □

   Nausea □

   Other complaints □

   Other complaints: _____

   1.2. Where do the complaints occur?

   Please name the location(s) or area(s) where the symptoms typically occur.

   Neck □

   Back □

   Jaw □

   Shoulder

   Right □ Left □ Both sides □

Arm

Right □ Left □ Both sides □

Chest □

Right □ Middle □ Left □

Behind the sternum □

Upper stomach pain

Right □ Middle □ Left □

Localization not clear □

1.3. How would you most likely describe the discomfort?

1.3.1. What is the nature of pain?

Pressure (dull) □

Stinging pain (sharp, pointed) □

Constricting, strangling □

Burning □

Unspecific □

No specification possible □

1.3.2. How large is the area of pain?

Rather punctiform (< 2€ coin) □

Rather areal (> 2€ coin) □

No specification possible □

1.3.3. In which situations do the complaints typically occur?

(Multiple answers possible)

Physical exertion □

Triggered by pressure □

Triggered by certain movements □

Breath dependent or when coughing □

At rest □

Under emotional stress □

Lying at night □

Another situation: _____

1.4. What is the course of the pain/ discomfort?

1.4.1. How does the pain/ discomfort begin?

Suddenly/ abruptly □

Increases over minutes □

1.4.2. How long does a pain/ complaint episode typically last?

Seconds □

1-30 minutes □

>30 minutes □

1.4.3. What relieves the discomfort?

Taking nitroglycerin □

Resting □

Other □

Other: _____

1.4.4. On average, how often do you have a pain/ complaint episode?

Several times a day □

Once a day □

Several times a week □

Once a week □

Less than once a week □

Unique event □

1.4.5. How long have you had these complaints?

For less than 1 week □

For 1-2 weeks □

For 2-4 weeks □

For 4-6 weeks □

For 6-8 weeks □

For >8 weeks to 6 months □

For 6-12 months □

For >12 months □

1.4.6. What is your explanation for the origin of the complaints?

Do you suspect the heart as the cause? □

Do you suspect muscles or the skeletal system as the cause? □

Do you suspect the stomach or the bowel as the cause? □

Do you suspect the lungs as the cause? □

Do you suspect another cause? □

2. Exercise Capacity

In the following section, we will ask you a few questions to help us assess your exercise capacity and physical endurance and therefore the severity of your complaints.

□ Even with the strongest physical exertion, no complaints occur.

□ No complaints during normal physical exertion such as walking fast on level ground or climbing stairs. However, complaints occur during strenuous or sudden physical exertion.

□ Complaints during moderate exertion in everyday life such as walking fast, walking uphill, emotional stress or during exertion after a meal or in cold temperatures. However, the complaints begin, for example, only after more than 400-500m of walking fast or after climbing more than one flight of ordinary stairs.

□ Complaints during mild exertion such as walking less than 400-500m or climbing one flight of stairs.

Complaints occur with the slightest physical activity (e.g. a few steps in the apartment).

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A.2. Evaluation of symptoms and angina type A.2.1. Definition of angina type

Assessment according to the Diamond-Forrester model, updated after Gender et al. in the version of the German National Disease Management Guideline „Chronic CAD" and ESC Guidelines on chronic coronary syndrome[1, 2]:

Criteria:

1. Constricting discomfort localized either behind the sternum or in the neck, shoulder, jaw, or arm.
    a. Character: Pressure, tightness AND
    b. Localization: Behind the sternum, neck, shoulder, jaw, or arm
2. Precipitated/ intensified by physical exertion or emotional stress
3. Relief of complaints by taking nitroglycerin or pausing physical activity within 5 minutes

Definition:

1. Typical angina pectoris: Meets all 3 characteristics
2. Atypical angina: Meets 2 of the 3 characteristics
3. Non-anginal chest pain: Meets ≤1 of the characteristics

A.2.2. Evaluating rules to define the type of chest pain

Definition of the criteria based on the questionnaire.

1. Criterion:
    a. Question 1.3.1.: Pressure (dull) or constricting, strangling AND
    b. Question 1.2.: Behind the sternum, neck, shoulder, jaw, or arm
2. Criterion:
    a. Question 1.3.3.: Response: Physical exertion OR Under emotional stress
3. Criterion:
    a. Question 1.4.3.: Response: Taking nitroglycerin OR Resting

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Table A1: Age, Gender and Symptom-based pretest-probability for the presence of an obstructive coronary artery disease according to the 2019 ESC guidelines on the diagnosis and management of chronic coronary syndrome

	Typical Angina		**Atypical Angina**		**Non-Anginal Chest Pain**		**Dyspnoea**	
Age (years)	Men	Women	Men	Women	Men	Women	Men	Women
30–39	3%	5%	4%	3%	1%	1%	1%	1%
40–49	22%	10%	10%	6%	3%	2%	3%	2%
50–59	32%	13%	17%	6%	11%	3%	11%	3%
60–69	44%	16%	26%	11%	22%	6%	22%	6%
70–79	52%	27%	34%	19%	24%	10%	24%	10%

Table A 1 – Age, Gender, and Symptom-based pre-test probability for the presence of an obstructive coronary artery disease according to the 2019 European Society of Cardiology guidelines for the diagnosis and management of chronic coronary syndrome. In case of concomitant chest pain and dyspnoea, the higher pre-test probability value was applied [2].

Table A2: Age, Gender, and Symptom-based pre-test probability for the presence of an obstructive coronary artery disease according to the German National Disease Management guideline on chronic coronary artery disease and the 2013 European Society of Cardiology Guidelines on the diagnosis and management of stable coronary artery disease.

	Typical Angina		**Atypical Angina**		**Non-Anginal Chest Pain**	
Age (years)	Men	Women	Men	Women	Men	Women
30–39	59%	28%	29%	10%	18%	5%
40–49	69%	37%	38%	14%	25%	8%
50–59	77%	47%	49%	20%	34%	12%
60–69	84%	58%	59%	28%	44%	17%
70–79	89%	68%	69%	37%	54%	24%
> 80	93%	76%	78%	47%	65%	32%

Table A 2 – Age, Gender and Symptom-based pretest-probability for the presence of an obstructive coronary artery disease according to the German National Disease Management guidelines on the diagnosis and management of stable coronary artery disease[1,3].

Table A3: Detailed Definition of guideline-adherence depending on pre-test probability and the performance or results of non-invasive image guided testing

Pretest-Probability	**Results of**				**Guideline Adherence**
	Coronary CT Angiography	**Stress Cardiac-MRI**	**Stress-Echocardio-graphy**	**Myokardial-Perfusion-Scintigraphy**	
2019 European Society of Cardiology guidelines on chronic coronary syndrome[2]					
	Not done	Not done	Not done	Not done	No
			Either		
<5%	Signs of stenosis or inconclusive	Signs of ischaemia or inconclusive	Signs of ischaemia or inconclusive	Signs of ischaemia or inconclusive	Yes
	No signs of stenosis	No signs of ischaemia	No signs of ischaemia	No signs of ischaemia	No
	Not done	Not done	Not done	Not done	No
			Either		
>5%	Signs of stenosis or inconclusive	Signs of ischaemia or inconclusive	Signs of ischaemia or inconclusive	Signs of ischaemia or inconclusive	Yes
	No signs of stenosis or inconclusive	No signs of ischaemia	No signs of ischaemia	No signs of ischaemia	No
Special Cases	• Pathologic Exercise-ECG with typical Angina CCS-class 3-4 • Typical Angina CCS-class 3-4 with wall motion abnormalities already at the resting echocardiography.				Yes
German National Disease Management Guideline on stable coronary artery disease[1]					
	Not done	Not done	Not done	Not done	No
			Either		
<15%	Signs of stenosis or inconclusive	Signs of ischaemia or inconclusive	Signs of ischaemia or inconclusive	Signs of ischaemia or inconclusive	Yes
	No signs of stenosis	No signs of ischaemia	No signs of ischaemia	No signs of ischaemia	No
	Not done	Not done	Not done	Not done	No
			Either		
15-85%	Signs of stenosis or inconclusive	Signs of ischaemia or inconclusive	Signs of ischaemia or inconclusive	Signs of ischaemia or inconclusive	Yes
	No signs of stenosis	No signs of ischaemia	No signs of ischaemia	No signs of ischaemia	No
>85%	irrespective	irrespective	irrespective	irrespective	Yes

The content of dissertation project IV has been published in Int J Cardiol Heart Vasc

Detailed Definition of guideline-adherence depending on pre-test probability and the performance or results of non-invasive image guided testing with either coronary CT-angiography, stress cardiac-MRI, stress-echocardiography or myocardial-perfusion-scintigraphy according to the 2019 European Guideline for the diagnosis and management of chronic coronary syndrome and the German National Disease Management Guideline on chronic coronary artery disease[1,2].

Table A4: Details on non-invasive image guided testing with guideline-adherent and guideline non-adherent coronary angiography

Parameter	Statistic	Total	Guideline-Adherent Coronary Angiography*	Guideline Non-Adherent Coronary Angiography	p-value
Total		426	87	339	
ECG at rest	n (%)	405 (95.1)	82 (94.3)	323 (95.3)	0.907
Echocardiography at rest	n (%)	342 (80.3)	65 (74.7)	277 (81.7)	0.189
LVEF >55%	n (%)	235 (76.3)	52 (89.7)	183 (73.2)	0.043
LVEF < 55%	n (%)	73 (23.7)	6 (10.3)	67 (26.8)	0.013
Wall motion disorders	n (%)	30 (8.8)	4 (6.2)	26 (9.4)	0.558
Exercise ECG	n (%)	79 (18.5)	18 (20.7)	61 (18.0)	0.673
Evidence of ischemia					0.138
negative	n (%)	24 (30.4)	6 (33.3)	18 (29.5)	
pathologic	n (%)	23 (29.1)	2 (11.1)	21 (34.4)	
inconclusive finding	n (%)	32 (40.5)	10 (55.6)	22 (36.1)	
Non-Invasive Image Guided Testing	n (%)	89 (20.9)	84 (96.6)	5 (1.5)	<0.001
Stress echocardiography	n (%)	8 (1.9)	5 (5.7)	3 (0.9)	0.011
Evidence of ischemia					0.018
pathologic	n (%)	4 (50.0)	4 (80.0)	0 (0.0)	
negative	n (%)	3 (37.5)	0 (0.0)	3 (100.0)	
inconclusive finding	n (%)	1 (12.5)	1 (20.0)	0 (0.0)	
Stress MRI	n (%)	18 (4.2)	17 (19.5)	1 (0.3)	<0.001
Evidence of ischemia					<0.001
pathologic	n (%)	15 (83.3)	15 (88.2)	0 (0.0)	
negative	n (%)	1 (5.6)	0 (0.0)	1 (100.0)	
inconclusive finding	n (%)	2 (11.1)	2 (11.8)	0 (0.0)	
Myocardial perfusion Scintigraphy	n (%)	35 (8.2)	34 (39.1)	1 (0.3)	<0.001
Evidence of ischemia					<0.001
pathologic	n (%)	26 (74.3)	26 (76.5)	0 (0.0)	
negative	n (%)	1 (2.9)	0 (0.0)	1 (100.0)	
inconclusive finding	n (%)	8 (22.9)	8 (23.5)	0 (0.0)	
Coronary CT-Angiography	n (%)	30 (7.0)	29 (33.3)	1 (0.3)	<0.001
Evidence of stenoses					0.801
Stenoses;	n (%)	21 (70.0)	20 (69.0)	1 (100.0)	
Stenoses cannot be assessed (highly calcified)	n (%)	6 (20.0)	6 (20.7)	0 (0.0)	
No clear finding;	n (%)	3 (10.0)	3 (10.3)	0 (0.0)	

Table A 4 – Details on non-invasive image guided testing with guideline-adherent and guideline non-adherent coronary angiography according to the European Guidelines for the diagnosis and management of chronic coronary syndrome2. If sums do not equal the total number of patients it is because of missing data.

CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention.

Table A5: Details on the results of the coronary angiography with evaluation of guideline-adherence

Parameter	Statistic	Total	Guideline-Adherent Coronary Angiography	Guideline Non-Adherent Coronary Angiography	p-value
FFR/ iFR/RFR performed					0.744
Yes (ischemia)	n (%)	14 (3.3)	4 (4.6)	10 (2.9)	
Yes (no ischemia)	n (%)	20 (4.7)	4 (4.6)	16 (4.7)	
Angiography Results					
1-vessel coronary disease	n (%)	79 (18.5)	12 (13.8)	67 (19.8)	0.124
2-vessel coronary disease	n (%)	77 (18.1)	18 (20.7)	59 (17.4)	
3-vessel coronary disease	n (%)	121 (28.4)	22 (25.3)	99 (29.2)	
Hypertensive heart disease	n (%)	4 (0.9)	2 (2.3)	2 (0.6)	
Exclusion of CAD	n (%)	83 (19.5)	15 (17.2)	68 (20.1)	
Coronary sclerosis without > 50% stenoses	n (%)	50 (11.7)	17 (19.5)	33 (9.7)	
Stenosed bypasses	n (%)	1 (0.2)	0 (0.0)	1 (0.3)	
Other.	n (%)	11 (2.6)	1 (1.1)	10 (2.9)	
Therapy Decision after diagnosis					0.399
No specific therapy	n (%)	83 (19.5)	14 (16.1)	69 (20.4)	
Optimized drug therapy	n (%)	166 (39.0)	31 (35.6)	135 (39.8)	
Revascularisation	n (%)	177 (41.5)	42 (48.3)	135 (39.8)	0.192
PCI	n (%)	158 (37.1)	36 (41.4)	122 (36.0)	
CABG	n (%)	19 (4.5)	6 (6.9)	13 (3.8)	

Table A 5 – Details on the results of the coronary angiography with evaluation of guideline-adherence according to the 2019 European Society of Cardiology guideline for the diagnosis and management of chronic coronary syndrome[2]. If sums do not equal the total number of patients it is because of missing data.

CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention.

References

1. Bundesärztekammer (BÄK), Kassenärztliche Bundesvereinigung (KBV), Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF) 2019. *National disease management guidelines for chronic CAD (NVL)—long version*, 5th edition. www.khk.versorgungsleitlinien.de (10 February 23).

2. Task Force Members: Montalescot G, Sechtem U, al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart* J 2013;**34**:2949–3003.

3. Knuuti J,Wijns W, Saraste A, , et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J* 2020;**41**:407–477.

Doctoral student's declaration of contribution

1. **Methods for assessing guideline adherence for invasive procedures in the care of chronic coronary artery disease: a scoping review**

   Hannah Kentenich, Dirk Müller, Bastian Wein, Stephanie Stock, Yana Seleznova

   BMJ Open [Impact Factor at time of publication: 3.007]

   Author's contributions

   Hannah Kentenich, Yana Seleznova and Dirk Müller were involved in the conception and design of this review. The selection of articles was carried out by Hannah Kentenich and Yana Seleznova, consulting DM as third reviewer in case of disagreement. The data extraction and analysis were conducted and guided by Hannah Kentenich and Yana Seleznova. All the authors contributed to the data interpretation. Hannah Kentenich and Yana Seleznova wrote the final manuscript. Bastian Wein, Dirk Müller and Stephanie Stock critically revised the final manuscript. All the authors read and approved the final manuscript. YS is responsible for the overall content as guarantor.

2. **Evaluation of guideline adherence for cardiac catheterization in patients with presumed obstructive coronary artery disease in Germany (ENLIGHT-KHK) – A multicentre, prospective, observational study**

   Yana Seleznova, Bastian Wein, Dirk Müller, Marie Naumann, Oliver Bruder, Melanie Steffen, Windhövel Ute, Simon Loeser, Jörg Artmann, Thomas Fritz, Melanie Eckardt, Stephanie Stock, Christoph Kurt Naber

   Cardiovascular Revascularization Medicine [Impact Factor at time of publication: 1.23]

Author's contributions

Yana Seleznova: Methodology, Investigation, Writing – original draft, Writing - review & editing. Bastian Wein: Methodology, Conceptualization, Project administration, Supervision, Writing - review & editing, Funding acquisition. Dirk Müller: Conceptualization, Methodology, Supervision, Writing - review & editing, Funding acquisition. Marie Naumann: Methodology, Writing - review & editing. Oliver Bruder: Conceptualization, Supervision. Melanie Steffen: Investigation. Ute Windhövel: Data curation, Funding acquisition. Simon Loeser: Conceptualization, Supervision, Funding acquisition. Jörg Artmann: Conceptualization, Investigation. Thomas Fritz: Funding acquisition. Melanie Eckardt: Investigation. Stephanie Stock: Supervision. Christoph Kurt Naber: Conceptualization, Funding acquisition.

3. Health economic consequences of optimal vs. observed guideline adherence of coronary angiography in patients with suspected obstructive stable coronary artery in Germany: a microsimulation model.

Yana Seleznova, Oliver Bruder, Simon Loeser, Jörg Artmann, Arim Shukri, Marie Naumann, Stephanie Stock, Bastian Wein*, Dirk Müller*

*Contributed equally

European Heart Journal - Quality of Care and Clinical Outcomes [Impact Factor at time of publication: 7.064]

Author's contributions

Yana Seleznova, Bastian Wein, Oliver Bruder and Dirk Müller initiated the study. Yana Seleznova, Dirk Müller and Bastian Wein designed the decision-analytic model, acquired, analyzed and interpreted the data. Yana Seleznova wrote the first draft of the manuscript. Dirk Müller and Bastian Wein revised the manuscript. Oliver Bruder, Simon Loeser, Jörg Artmann, Stephanie Stock and Arim Shukri advised the analysis and interpretation of the data. All authors read and approved the final manuscript.

4. **Evaluation of the guideline-adherence of coronary angiography in patients with suspected chronic coronary syndrome – Results from the German prospective multicentre ENLIGHT-KHK project**

Bastian Wein, Yana Seleznova, Dirk Müller, Marie Naumann, Simon Loeser, Jörg Artmann, Thomas Fritz, Melanie Steffen, Ute Windhövel, Michael Haude, Juergen vom Dahl, Ulrich Schaefer, Moritz Montenbruck, Markus Zarse, Ruediger Jegodka, Thorsten Dill, Jan-Erik Guelker, Dirk Boese, Oliver Bruder

International Journal of Cardiology: Heart & Vasculature [Impact Factor at time of publication: 2.9]

Author's contributions

Yana Seleznova advised (i) the conceptualization and methodology of construct guideline adherence, (ii) the analysis and interpretation of the data, and (iii) revised the manuscript.

Übersicht der Publikationen:

1. Kentenich H, Müller D, Wein B, Stock S, Seleznova Y. Methods for assessing guideline adherence for invasive procedures in the care of chronic coronary artery disease: a scoping review. *BMJ Open* 2023;**13**:e069832.
2. Seleznova Y, Wein B, Muller D, et al. Evaluation of Guideline Adherence for Cardiac Catheterization in Patients With Presumed Obstructive Coronary Artery Disease in Germany (ENLIGHT-KHK) - A Multicentre, Prospective, Observational Study. *Cardiovasc Revasc Med* 2021;**31**:19–25.
3. Seleznova Y, Bruder O, Loeser S, et al. Health economic consequences of optimal vs. observed guideline adherence of coronary angiography in patients with suspected obstructive stable coronary artery in Germany: a microsimulation model. *Eur Heart J Qual Care Clin Outcomes* 2023 Mar 9:qcad015.
4. Wein B, Seleznova Y, Mueller D, et al. Evaluation of the guideline-adherence of coronary angiography in patients with suspected chronic coronary syndrome – Results from the German prospective multicentre ENLIGHT-KHK project. *Int J Cardiol Heart Vasc* 2023;**46**:101203.

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