








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 ^{1,*}, Oliver Bruder ^{2,3}, Simon Loeser⁴, Jörg Artmann⁴, Arim Shukri ¹, Marie Naumann ¹, Stephanie Stock ¹, Bastian Wein ^{2,5,†} and Dirk Müller ^{1,†}

¹Institute for Health Economics and Clinical Epidemiology, Faculty of Medicine and University Hospital Cologne, University of Cologne, Gleueler Straße 176-178, 50935 Cologne, Germany; ²Department of Cardiology and Angiology, Contilia Heart and Vascular Center, Elisabeth-Krankenhaus Essen, Klara-Kopp-Weg 1, 45138 Essen, Germany; ³Faculty of Medicine, Ruhr University Bochum, 44801, Bochum, Germany; ⁴AOK Rheinland/ Hamburg, Kasernenstraße 61, 40213 Düsseldorf, Germany; and ⁵Department of Cardiology, Faculty of Medicine, University of Augsburg, Stenglinstrasse 2, 86156, Augsburg, Germany

Received 14 January 2023; revised 10 February 2023; accepted 7 March 2023; online publish-ahead-of-print 9 March 2023

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.

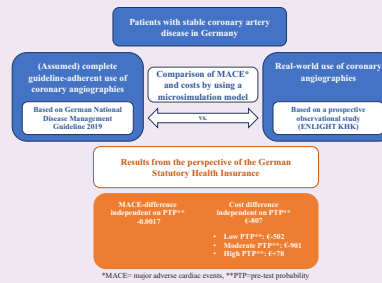
† Contributed equally.

* Corresponding author: Yana Seleznova, Tel: +0049221-48730908; Email: yana.seleznova@uk-koeln.de

© The Author(s) 2023. Published by Oxford University Press on behalf of the European Society of Cardiology. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (<http://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

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.



Keywords

Coronary angiography • Guideline adherence • Chronic coronary artery disease • Economic evaluation • Costs

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), stress-echocardiography (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 evidence¹¹ 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 'real-world 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 analyses¹⁷—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.

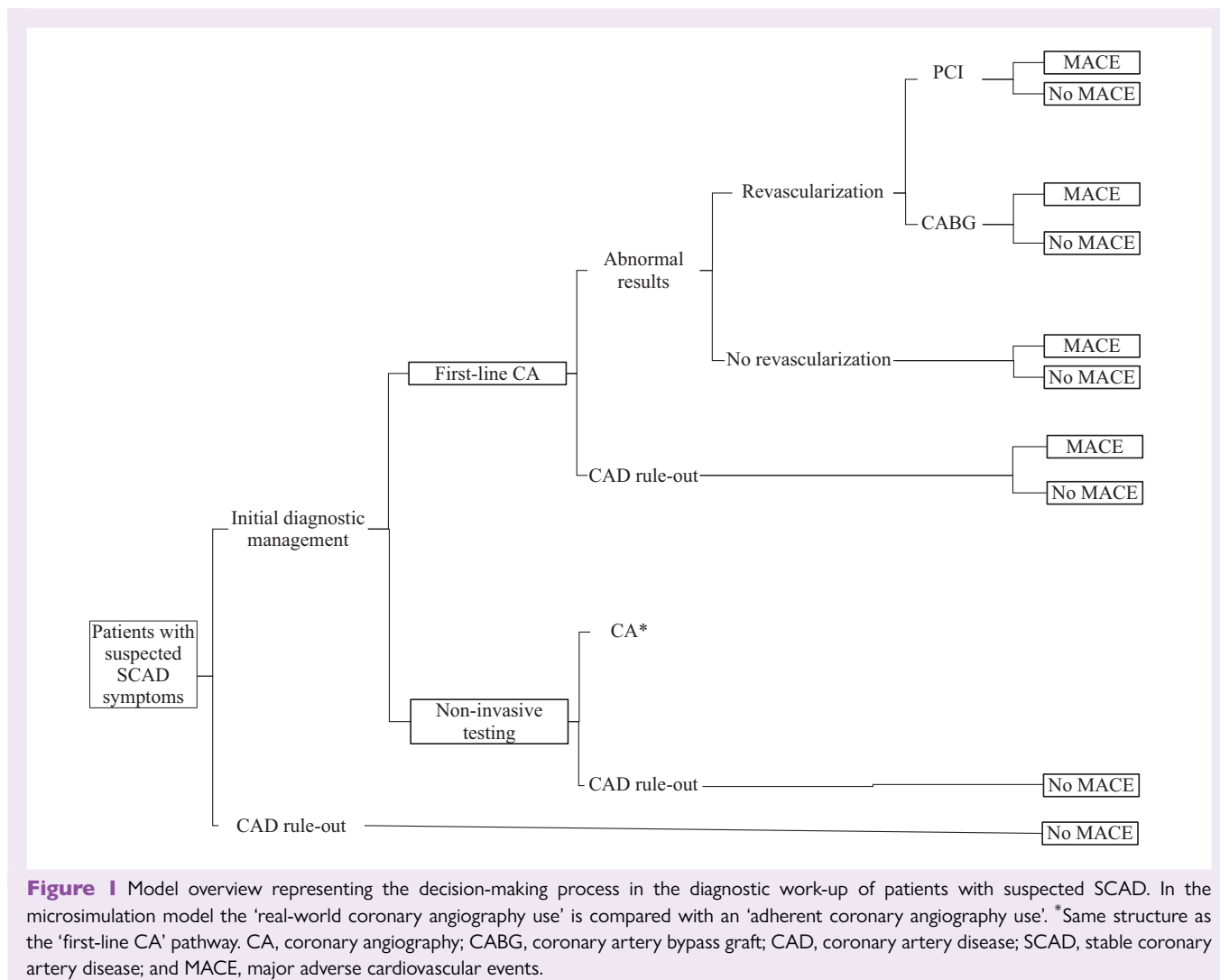
Patient population and comparators

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 model²⁵ 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).

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 SCAD² (without being updated for the 2019 ESC guidelines²⁶). 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).

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.

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; and PTP, pre-test probability.

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 GNDMG³). Table 2 lists the clinical input data.

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 SHIs¹⁵ (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 GOP³²).

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. EBM³¹ and GOP³²). 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 inflation²¹ with respect to the German harmonised index of consumer prices³³ 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.

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 efforts³⁶).

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).

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

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; and 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.

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.

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 ESC²⁶ 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, €2534³⁷).

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

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
CA outpatient ^a	0.235 [0.193, 0.277]	
CA with FFR ^b	0.079 [0.059, 0.099]	Patients' records from nine participating hospitals
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 [33, 39]	
PCI ^j	4128 [3992, 4256]	
CABG ^k	18 506 [17 233, 20 174]	
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; and 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

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 €400³¹), one-third of an inpatient CA (€2534³⁷), or is even higher than the costs for any NIT w/o eECG (e.g. cCTA³²). 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.

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; and PTP, pre-test probability.
^a ‘Adherent CA-use’ is less costly and more effective in averting MACE compared with ‘real-world CA-use’.

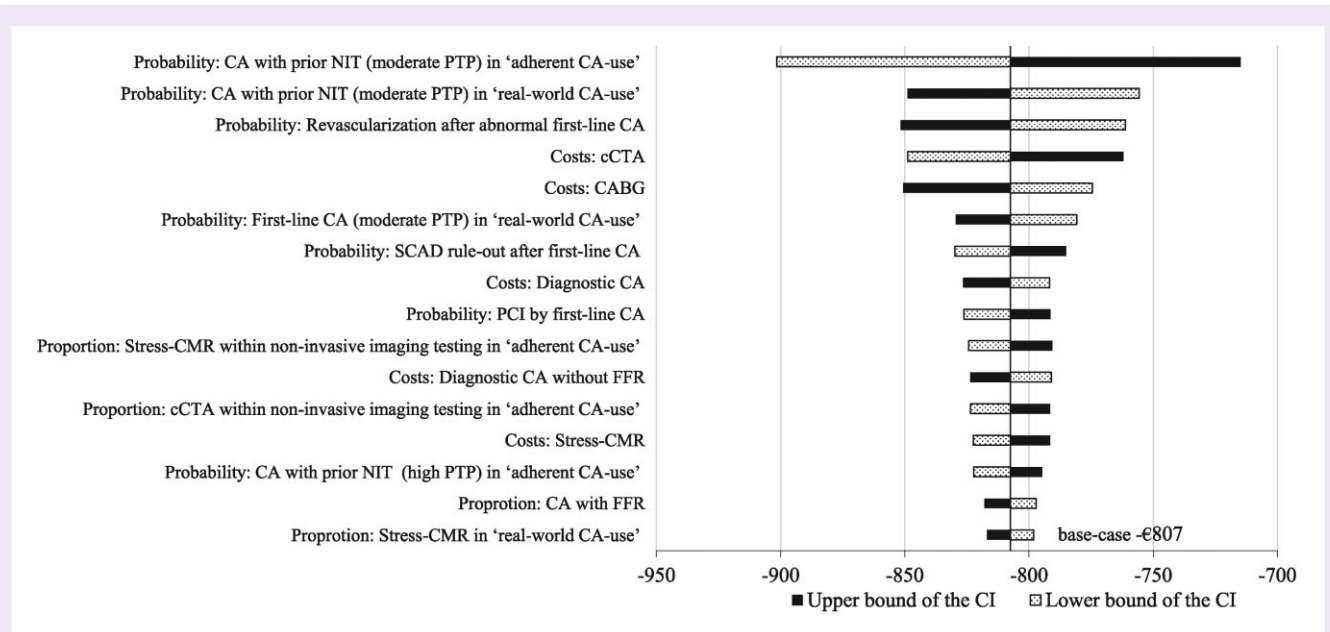


Figure 2 Tornado-diagram presenting the results of the univariate deterministic sensitivity analysis (i.e. parameters with the greatest impact on incremental costs). CA, coronary angiography; CABG, coronary artery bypass grafting; cCTA, coronary computed tomography angiography; CI, confidence interval; CMR, cardiac magnetic resonance; FFR, fractional flow reserve; NIT, non-invasive testing; PCI, percutaneous coronary intervention; PTP, pre-test probability; and SCAD, stable coronary artery disease.

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 positive³ 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 Germany⁴ 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 ENLIGHT-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 non-comparative 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 obesity⁴³ 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 patients⁴⁸ 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 ASS⁴⁹ 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.

Acknowledgements

We would like to especially thank Dr Ute Windhövel from the Cardiovascular European Research Center (CERC) Deutschland GmbH for collecting and managing data according to the International Conference on Harmonisation-Good Clinical Practice guidelines and German data protection regulations.

Special thanks to the whole ENLIGHT-KHK study and recruitment teams who kept the trial ongoing despite the many obstacles and challenges during the COVID-19 pandemic. We thank all the patients who were willing to participate in this trial.

Funding

Innovation Committee at the Federal Joint Committee (Gemeinsamer Bundesausschuss (GBA) [grant number 01VSF17011]; Erfassung und Optimierung der Leitlinienadhärenz im Indikationsstellungsprozess zur Herzkatheteruntersuchung bei stabiler Koronarer Herzkrankung (ENLIGHT-KHK) [to Y.S., M.N., and D.M.]. Innovation Committee at the GBA is a public funding institution that is co-financed by the German Statutory Health Insurance. GBA is the highest decision-making body of the joint self-government of physicians, dentists, hospitals and health insurance funds in Germany.

Conflicts of Interest: None declared.

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.

Ethics and dissemination

This study received a leading Ethics Approval (2018/12/13) from the ethics committee of the Medical Association of North Rhine (Ärztekammer Nordrhein) (Nr. 2 018 361).

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

- Genders TSS, Steyerberg EW, Alkadhi H, Leschka S, Desbiolles L, Nieman K et al. A clinical prediction rule for the diagnosis of coronary artery disease: validation, updating, and extension. *Eur Heart J* 2011;**32**:1316–1330.
- 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.
- 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).
- Deutsche Herzstiftung 2020. 32. Deutscher Herzbericht. <https://www.herzstiftung.de/system/files/2021-06/Deutscher-Herzbericht-2020.pdf> (10 February 23).
- Mühlberger V, Kaltenbach L, Bates K, Ulmer H. Austrian National Cardiac Catheterization Laboratory Registry OKG: cardiac catheterization in Austria: results from the Austrian National Cardiac Catheterization Laboratory Registry (ANCLAR) 2012–2018. *Wien Klin Wochenschr* 2020;**132**:79–89.
- 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.
- Fugilla 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.
- 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, 231–254.
- Dissmann W, De Ridder M. The soft science of German cardiology. *Lancet* 2002;**359**:2027–2029.
- 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 Gesundheitswes* 2017;**127–128**:62–71.
- Frank-Tewaag J, Bleek J, Günster C, Schneider U, Horenkamp-Sonntag D, Marschall U 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.
- Institute for Quality Assurance and Transparency in Healthcare (IQTiG) 2021. Bundesqualitätsbericht 2021. QS-verfahren percutane koronarintervention (PCI) und koronarangiographie. Erfassungsjahre 2019 und 2020. <https://iqtig.org/veroeffentlichungen/bundesqualitaetsbericht/> (22 December 22).
- Timmis A, Vardas P, Townsend N, Torbica A, Katus H, De Smedt D et al. European Society of Cardiology: cardiovascular disease statistics 2021. *Eur Heart J* 2022;**43**:716–799.
- Baldus S, Werdan K, Levenson B, Kuck KH. Klug entscheiden... In der Kardiologie. *Dtsch Arztebl International* 2016;**113**:1312–1315.
- Seleznova Y, Wein B, Müller D, Naumann M, Bruder O, Steffen M 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, El Sabbagh A, Park JY, Crusan D 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, De Bekker-Grob E, Briggs AH, Carswell C 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, Bonetti PO, Osswald S, Linka A 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, Zellweger MJ, Jeger R, Buser PT et al. Cost-effectiveness 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.
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, Nabhan AF. 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, Capodanno D, Barbato E, Funck-Brentano C 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, Prescott E, Ballo H, Bax JJ 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/artztgruppen_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&sachschlüssel = CC13-06*&zeitscheiben = 3#abreadcrumb (22 December 22).
34. Moschetti K, Kwong RY, Petersen SE, Lombardi M, Garot J, Atar D 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, Bui KHa, Buylova Gola A, Chiribiri A 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/drugs/F49G> (22 December 22).
38. Cabana MD, Rand CS, Powe NR, Wu AW, Wilson MH, Abboud P-AC 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, Contreras JAP, Borrero AMP, Patiño-Lugo DF 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. Hoon CJGM, Crijs HJGM, Dierckx-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 J-F, Bonello L, Sarran A, Tron C, Christiaens 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, Kaufmann PA, Le Guludec D, Perrone Filardi P 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, P. Howard J, Rajkumar C, Nowbar AN, Kane C, Mahdi D 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, Bangalore S, O'brien SM, Boden WE 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, Maron DJ, Spertus JA, Mancini GBJ et al. Effect of PCI on long-term survival in patients with stable ischemic heart disease. *N Engl J Med* 2015;**373**:1937–1946.
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, Yuan F, Bangdiwala SI, Bosch J et al. The cost-effectiveness 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).