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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.

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.

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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)

1. Introduction

The 2019 European Society of Cardiology (ESC) Guidelines (GL) for the diagnosis and management of Chronic Coronary Syndrome (ESC-CCS-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 [1] prospectively evaluated the degree of GL-adherence, [2] assessed health economic consequences of potential deviations in GL-adherence and [3] 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].

2. Methods

2.1. 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).

2.2. 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 work-up at which the patients were included. These cohorts were: [1] patients referred for elective CA, [2] patients presenting at the emergency department who underwent CA, [3] patients presenting in the outpatient department without prior diagnostic work-up, [4] patients presenting at the emergency department undergoing planned non-invasive testing, and [5] 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).

2.3. 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

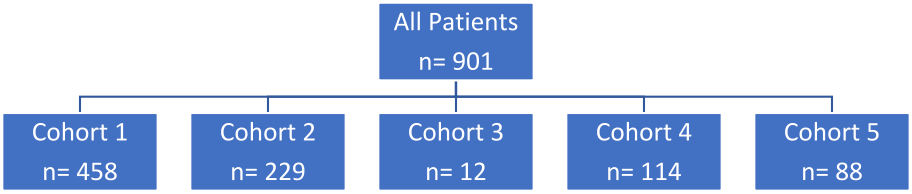

Fig. 1. Number of patients with clinical suspicion of obstructive coronary artery disease without acute myocardial infarction who were included in the study and grouped into five predefined cohorts – two main (1 and 2) and three sub-cohorts (3, 4 and 5). The distinct cohorts were: [1] patients undergoing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

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 Chronic 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

Table 1 – 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.

Table 2
Assessment of guideline-adherence of coronary angiography depending on pre-test 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

Table 2 – 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].

were collected by a self-designed standardized patient questionnaire. Symptoms were categorized into typical angina, atypical angina, non-anginal 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.

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.

2.4. 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 Chi-square 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).

3. Results

3.1. 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).

3.2. 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 non-invasive testing).

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.

3.3. Guideline-adherence of CA

Among the study population, 20.4 % of the CAs were GL-adherent

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/m^2	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)	193/334 (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 (%)	32/426 (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)	

Table 3 – 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 m^2. CABG – Coronary Artery Bypass Grafting, CAD – Coronary Artery Disease, PCI – Percutaneous Coronary Intervention.

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

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 according to the 2019 European Society of Cardiology Guideline for the diagnosis and management of chronic coronary syndrome [2]. * Based on the patient questionnaire.

Table A1
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.

	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 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, respectively.[1], [3].

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 %.

3.4. 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

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	Myocardial-Perfusion-Scintigraphy	
2019 European Society of Cardiology guidelines on chronic coronary syndrome[2]					
<5 %	Not done	Not done	Not done	Not done	No
	Either				Yes
	Signs of stenosis or inconclusive	Signs of ischaemia or inconclusive	Signs of ischaemia or inconclusive	Signs of ischaemia or inconclusive	
	No signs of stenosis	No signs of ischaemia	No signs of ischaemia	No signs of ischaemia	No
>5 %	Not done	Not done	Not done	Not done	No
	Either				Yes
	Signs of stenosis or inconclusive	Signs of ischaemia or inconclusive	Signs of ischaemia or inconclusive	Signs of ischaemia or inconclusive	
	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				Yes
	Typical Angina CCS-class 3–4 with wall motion abnormalities already at the resting echocardiography.				
German National Disease Management Guideline on stable coronary artery disease[1]					
<15 %	Not done	Not done	Not done	Not done	No
	Either				Yes
	Signs of stenosis or inconclusive	Signs of ischaemia or inconclusive	Signs of ischaemia or inconclusive	Signs of ischaemia or inconclusive	
	No signs of stenosis	No signs of ischaemia	No signs of ischaemia	No signs of ischaemia	No
15–85 %	Not done	Not done	Not done	Not done	No
	Either				Yes
	Signs of stenosis or inconclusive	Signs of ischaemia or inconclusive	Signs of ischaemia or inconclusive	Signs of ischaemia or inconclusive	
	No signs of stenosis	No signs of ischaemia	No signs of ischaemia	No signs of ischaemia	No
>85 %	irrespective	irrespective	irrespective	irrespective	Yes

Table A 3 – 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 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.

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.

3.5. *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.

4. Discussion

4.1. *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/m^2) 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 ESC-CCS-GL-recommended NIGT prior to CA, an additional 18.5 % of patients at least received an exercise-ECG. These findings are in direct

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
	n	426	87	339	
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)	
Revascularization	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.*

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 non-diagnostic 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 non-adherence, 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].

4.2. 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.

5. Limitations

First, the initial patient recruitment target could not be achieved due to several factors: [1] restrictions on patient recruitment during the COVID-19 pandemic, [2] a cost covering study fee which could not compete with that of industry-sponsored trials, [3] 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 [5] due to funding restraints, the recruitment period could not be extended beyond 32 months. As a result, the a priori defined recruitment target of 1500 patients for the overall study cohort had to be re-evaluated, 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 insurees 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 non-adherent, overall GL-adherence rate would have even further dropped to 17.1 %.

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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Appendix

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).

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 Coronary Artery Disease" and the 2019 European Society of Cardiology 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

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

A.3. Tables

See Table A1, Table A2, Table A3, Table A4, Table A5.

References

[1] Bundesärztekammer (BÄK) KBK, Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF). Nationale VersorgungsLeitlinie Chronische KHK – Langfassung, 5. Auflage. Version 2019. [Available from: www.khk.versorgungsleitlinien.de]. Last accessed 10 February 2023.

[2] J. Knuuti, W. Wijns, A. Saraste, D. Capodanno, E. Barbato, C. Funck-Brentano, et al., 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes, Eur. Heart J. 41 (3) (2019) 70.

[3] G. Montalescot, U. Sechtem, S. Achenbach, F. Andreotti, C. Arden, A. Budaj, 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. 34 (38) (2013) 2949–3003.

[4] H. Figulla, A. Lauten, L. Maier, U. Sechtem, S. Silber, H. Thiele, Percutaneous Coronary Intervention in Stable Coronary Heart Disease -Is Less More? Deutsches Arzteblatt international. 117 (9) (2020).

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

[6] V. Muhlberger, H. Ulmer, L. Kaltenbach, O. Pachinger, 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. 22 (1–2) (1–2):22–6 (2015).

[7] M.S.J. Moeckel, E. Jeschke, Indikation, Prognose und regionale Unterschiede der Herzkatheterversorgung in Deutschland. Versorgungs-Report 2013/2014 - Schwerpunkt Depression. Stuttgart: Klauber, J.; Guenster, C.; Gerste, B.; Robra, BP.; Schmacke, N.; 2014. p. 231-54.

[8] J. Frank-Tewaag, J. Bleek, C. Günster, U. Schneider, D. Horenkamp-Sonntag, U. Marschall, et al., Regional variation in coronary angiography rates: the association with supply factors and the role of indication: a spatial analysis, BMC Cardiovasc. Disord. 22 (1) (2022).

[9] S. Piedmont, E. Swart, R. Kenmogne, R. Braun-Dullaeus, B. Robra, Left-heart catheterization followed by other invasive procedures: Regional comparisons reveal peculiar differences, Fortbildung und Qualitaet im Gesundheitswesen, Zeitschrift fur Evidenz, 2017, pp. 127–128.

[10] S. Baldus, K. Werdan, B. Levenson, K.H. Kuck, Klug entscheiden: in der Kardiologie, Detusches Ärzteblatt. 113 (27–28) (2016) 3.

[11] Y. Seleznova, B. Wein, D. Müller, M. Naumann, O. Bruder, M. Steffen, 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. Cardiovascular revascularization medicine : including molecular interventions. 2020.

[12] H. Möllmann, D.M. Leistner, P.C. Schulze, U. Sechtem, J. Bauersachs, Kommentar zu den Leitlinien (2019) der ESC zum chronischen Koronarsyndrom, Kardiologe 14 (6) (2020) 482–491.

[13] J. Klein, O. von dem Knesebeck, Inequalities in health care utilization among migrants and non-migrants in Germany: a systematic review, Int. J. Equity Health 17 (1) (2018) 160.

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

[15] A. Tchicaya, M. Braun, N. Lorentz, C. Delagardelle, J. Beissel, D. Wagner, Social inequality in awareness of cardiovascular risk factors in patients undergoing coronary angiography, Eur. J. Prev. Cardiol. 20 (5) (2013).

[16] P. Maurovich-Horvat, M. Bosserdt, K.F. Kofoed, N. Rieckmann, T. Benedek, et al., CT or Invasive Coronary Angiography in Stable Chest Pain, N. Engl. J. Med. 386 (17) (2022) 1591–1602.

[17] S.M. Bradley, J.A. Spertus, K.F. Kennedy, B.K. Nallamothu, P.S. Chan, M.R. Patel, 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. 174 (10) (2014) 1630–1639.

[18] M. Al-Hijji, R. Lennon, R. Gulati, A. El Sabbagh, J. Park, D. Crusan, et al., Safety and Risk of Major Complications With Diagnostic Cardiac Catheterization, Circ. Cardiovasc. Interv. 12 (7) (2019).

[19] C. Chmiel, O. Reich, A. Signorell, R. Tandjung, T. Rosemann, O. Senn, Appropriateness of diagnostic coronary angiography as a measure of cardiac ischemia testing in non-emergency patients - a retrospective cross-sectional analysis, PLoS One 10 (2) (2015).

[20] C. Chmiel, O. Reich, A. Signorell, S. Neuner-Jehle, T. Rosemann, O. Senn, 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 8 (11) (2018).

[21] AOK Bundesverband. Zahlen und Fakten 2020; [Available from: https://www.aok-bv.de/imperia/md/aokbv/aok/zahlen/zuf 2020 web.pdf]. Last accessed 10 February 2023.