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Guideline adherence in the use of coronary angiography in patients presenting at the emergency department without myocardial infarction – Results from the German ENLIGHT-KHK project☆

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ABSTRACT

Background: For patients with acute myocardial infarction (AMI), direct coronary angiography (CA) is recommended, while for non-AMI patients, the diagnostic work-up depends on clinical criteria. This analysis provides initial prospective German data for the degree of guideline-adherence (GL) in the use of CA on non-AMI patients presenting at the emergency department (ED) with suspected acute coronary syndrome (ACS) according to the 2015 ESC-ACS-GL. Furthermore the implications of the application of the 2020 ESC-ACS-GL recommendations were evaluated.

Methods: Patient symptoms were identified using a standardized questionnaire; medical history and diagnostic work-up were acquired from health records. In accordance with the 2015 ESC-ACS-GL, CA was considered GL-adherent if intermediate risk criteria (IRC) were present or non-invasive, image-guided testing (NIGT) was pathological.

Results: Between January 2019 and August 2021, 229 patients were recruited across seven centers. Patients presented with chest pain, dyspnea, and other symptoms in 66.7%, 16.2% and 17.1%, respectively, were in mean 66.3 ± 10.5 years old, and 36.3% were female. In accordance with the 2015 ESC-ACS-GL, the use of CA was GL-

Abbreviations: AMI, Acute myocardial infarction; CA, Coronary angiography; CAD, Coronary artery disease; ED, Emergency Department; ESC, European Society of Cardiology; ESC-ACS-GL, European Society of Cardiology guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation; ESC-CCS-GL, European Society of Cardiology guidelines for the management of chronic coronary syndromes; GL, Guideline; GRACE Score, Global Registry of Acute Coronary Events 2.0 score; IRC, Intermediate risk criteria; MRI, Magnetic resonance imaging; NIGT, Non-invasive image guided testing; NSTEMI, Non-ST-segment-elevation myocardial infarction; PCI, Percutaneous coronary intervention; PTP, Pretest probability; SHI, Statutory health insurance company; STEMI, ST-segment-elevation myocardial infarction.

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adherent for 64.0% of the patients. GL-adherent compared to non-adherent use of CA resulted in revascularization more often (44.5% vs. 17.1%, $p < 0.001$). Applying the 2020 ESC-ACS-GL, 20.4% of CA would remain GL-adherent.

Conclusions: In the majority of cases, the use of CA was adherent to the 2015 ESC-ACS-GL. With regard to the 2020 and 2023 ESC-ACS-GL, efforts to expand the utilization of NIGT are crucial, especially as GL-adherent use of CA is more likely to result in revascularization.

(German Clinical Trials Register DRKS00015638; https://drks.de/search/de/trial/DRKS00015638; (registration date: 19 February 2019))

1. Introduction

Germany has the highest per capita volume of coronary angiographies (CAs) in Europe (approximately 900.000 CA in total per year and 1 in 112 citizens, respectively), 1.7 times higher than second-placed Austria [1,2]. These international as well as interregional differences have led to a longstanding debate on the overuse of CAs in Germany [2–4]. About one third of the annual CAs are performed on patients with an acute ST-segment-elevation or non-ST-segment-elevation myocardial infarction (STEMI, NSTEMI) and are therefore unquestionably adherent to the respective European Society of Cardiology (ESC) Guidelines (GL) [5–7]. However, the other two thirds of the annual CA volume are accounted for by patients without an AMI [2].

In the population of patients presenting at the emergency department with suspected acute coronary syndrome but without a STEMI, according to the 2015 ESC GL on ACS without persistent ST-segment-elevation (ESC-ACS-GL), direct CA is only recommended for patients with NSTEMI, (very) high, or intermediate risk criteria (IRC) (e.g. diabetes mellitus or prior revascularization) [7]. Where indicated, all other patients should primarily undergo non-invasive image-guided testing (NIGT) using coronary CT-angiography or either stress-echocardiography, myocardial perfusion scintigraphy or stress cardiac magnetic resonance imaging (MRI) [7]. The 2020 and the latest 2023 ESC-ACS-GL further strengthened the importance of NIGT in patients without very high or high risk criteria by recommending an algorithmic diagnostic work-up primarily using NIGT, where clinically indicated [8,9]. With this selective invasive approach invasive CA is only indicated if NIGT revealed coronary stenosis or myocardial ischemia [8,9].

Although multifactorial overuse of CA is at debate in Germany, no prospective data has yet been published on the degree of GL adherence in the use of CA on patients without an AMI (STEMI or NSTEMI) [2,3]. And this despite the fact, that about 10% of the annual CA volume in Germany is performed in this population [10]. To fill this gap in evidence, to evaluate the health-economic consequences of GL non-adherent use of CA, and to detect facilitators and barriers of GL-adherent care the multi-facetted ENLIGHT-KHK project was conducted [11]. Results on GL-adherence in the use of CA in chronic coronary syndrome (CCS), on health economic consequences and on factors influencing GL-adherence were already published [12–14].

The aim of this sub-analysis is to provide focused prospective evidence on the degree of GL adherence (according to the 2015 ESC-ACS-GL) with regard to the use of CA in patients who presented at the ED with symptoms potentially attributable to myocardial ischemia and had an AMI excluded prior to CA. During the recruitment period, the 2020 ESC-ACS-GL were published, which placed a much higher priority on NIGT in the diagnostic work-up of this population, as do the 2023 ESC-ACS-GL [6,9]. For the successful implementation of new guideline recommendations into clinical practice, evidence on the current practice and the implications of the new recommendations is crucial to develop appropriate and multifaceted intervention strategies [15]. Therefore we additionally evaluated the hypothetical implications of the application of the 2020 ESC-ACS-GL on CA GL-adherence rates in comparison to the 2015 ESC-ACS-GL in this defined population [6,7].

2. Methods

2.1. Study design

ENLIGHT-KHK, a prospective, strictly observational, and multicenter study, which recruited patients in the German federal states of North Rhine-Westphalia and Hamburg who were insured by the statutory health insurance (SHI) companies AOK Rheinland-Hamburg or AOK NORDWEST. The seven participating centers were all non-university hospitals that provided 24/7 catheterization laboratory services for AMI care as well as elective inpatient or outpatient diagnostic CA. The mean annual volume of CAs performed at each study center was 1880 (range: 830 to 4500; median: 1330). All the patients provided their informed, written consent. The study was conducted in accordance with the declaration of Helsinki, approved by the local ethics committees, and registered in the German Clinical Trials Registry (DRKS00015638).

2.2. Study population

This prespecified sub-analysis focused on the cohort of patients who presented at the ED with symptoms potentially attributable to acute myocardial ischemia (e.g. chest pain or dyspnea), had an AMI excluded with high-sensitivity Troponin levels being below the assay specific upper limits of normal, and did not display high risk criteria as outlined in appendix Table A1. All the patients underwent CA (with or without prior NIGT) on the discretion of the treating physicians. Patients with signs and symptoms of congestive heart failure or a left ventricular ejection fraction below 40% were excluded.

2.3. Data collection

Patient symptoms at the time of admission were derived from a self-designed, standardized patient questionnaire. Symptoms were categorized into typical angina, atypical angina, non-anginal chest pain and dyspnea based on the definitions and wordings of the 2019 ESC-CCS-GL and the German National Disease Management Guideline on chronic coronary artery disease (CAD) [8,16]. Pretest-probability (PTP) using age, gender and symptom category was derived according to the 2019 ESC-CCS-GL (see Appendix chapter 11.1 and Table A2 for details) [8].

Further patient information, their prior medical history and diagnostic work-up prior to the CA were taken from the medical records. The NIGT results were classified as either pathological (if signs of ischemia or relevant coronary artery stenosis were observed), non-pathological or inconclusive. The Global Registry of Acute Coronary Events 2.0 Score (GRACE Score) for determining in-hospital mortality risk in patients with ACS was only considered if documented in the medical records of the patient in question [17]. As a safety end-point the periprocedural complications cardiac death, procedure associated myocardial infarction or stroke as well as clinically relevant access site complications, i.e. those requiring medical or surgical intervention, were recorded.

2.4. Definition of guideline adherence

CA GL adherence was evaluated using the 2015 ESC-ACS-GL [7]. A CA was considered GL-adherent if the patient had one of the following

Table 1
Assessment of Guideline Adherence of Coronary Angiography. Assessment of guideline adherence of coronary angiography (in patients without very high or high risk criteria and high-sensitivity troponin levels below the upper limits of normal) in accordance with the 2015 and 2020 Guidelines on Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation and 2019 Guidelines on the diagnosis and management of Chronic Coronary Syndromes.5,7,8 *Stress echocardiography, myocardial perfusion scintigraphy, coronary CT angiography, stress magnet resonance imaging; **Intermediate risk criteria: diabetes mellitus, renal insufficiency (eGFR < 60 ml/min/1,73 m^2), congestive heart failure with an ejection fraction < 40%, early post-infarction angina (<3 months after AMI), prior revascularization or, if documented, a GRACE Score of 110–139; ***Although patients with pretest probability of < 5% should not undergo further testing, if clinical judgement indicated non-invasive testing and if this revealed signs of stenosis or ischemia, consecutive coronary angiography was considered guideline-adherent.

	Results of Non-Invasive Image Guided Testing*	Guideline Adherence of Invasive Coronary Angiography
2015 Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation Guidelines[5]		
Intermediate risk criteria present**	Irrespective of non-invasive testing	Yes
Intermediate risk criteria not present**	Pathological or inconclusive	Yes
	Non-pathological	No
2020 Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation Guidelines, according to the 2019 Diagnosis and Management of Chronic Coronary Syndromes Guidelines[7,8]		
Pretest probability < 5%	Not conducted or non-pathological	No
	Pathological or inconclusive***	Yes
Pretest probability > 5%	Not conducted or non-pathological	No
	Pathological or inconclusive***	Yes

IRC: diabetes mellitus, renal insufficiency (eGFR < 60 ml/min/1.73 m2), early post-infarction angina (<3 months after AMI), prior revascularization, or a GRACE-Score between 110 and 139 (if documented in the patient's medical records) [7]. If no IRC were present, the CA was deemed GL-adherent if the results of the preceding NIGT were pathological, or at least inconclusive [7].

Since the 2020 ESC-ACS-GL (which recommend the diagnostic work-up as outlined in the 2019 ESC-CCS-GL for this study population) were published during the recruitment period, GL adherence as per the 2019 ESC-CCS-GL was evaluated, too [6,8]. A CA was considered GL-adherent according to these GL, if a prior NIGT revealed ischemia or a stenosis in patients with a PTP of > 5% [8]. In order to respect clinical judgement, CAs were also considered GL-adherent if the patient in question had a PTP > 5% and NIGT revealed an inconclusive finding, or a PTP < 5% (for whom testing would not be recommended) but a pathological or inconclusive result in NIGT. Definitions of CA GL adherence according to the respective GL recommendations are summarized in Table 1.

2.5. 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, the 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, as appropriate. The association between guideline adherence and a set of covariates was assessed using logistic regression analysis. In order to assess factors that could potentially influence clinical likelihood – and therefore decision-making – several covariates were considered, such as age, gender and country of origin (as patients with a migratory background might confer a higher risk of inappropriate treatment) [18]. Furthermore, the referral pattern was taken into account, as differences in expertise might influence GL adherence. Both univariable and multivariable analyses were conducted. The results of the logistic regression are presented as odds ratios (OR) and the corresponding 95% confidence interval (CI). All tests were two tailed, and a p-value of < 0.05 was considered the threshold for statistical significance. All the analyses were conducted in R, version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Patient characteristics

In total, 229 patients were recruited for this cohort across seven study centers between January 2019 and August 2021. Considering the interruptions in patient recruitment due to COVID-19 pandemic regulations and different site initiation dates, patients were consecutively recruited over 5 to 30 months (in mean 15.6 months per center, median 11 months).

In accordance with the inclusion criteria, the patients presented at the ED with suspected acute coronary syndrome, had an AMI excluded, and underwent CA. Data collection for the determination of GL adherence was completed for 228 of the 229 patients. The patients were 66.3 ± 10.5 years old, 36.3% of them were female, 19.8% had a history of AMI, and 46.9% had prior revascularization. 22.9% of the patients presented at the ED via ambulance, 24.7% as walk-in patients, and 33.6% were referred by their family doctor (see Table 2 for details).

3.2. Presenting symptoms, diagnostic work-up and results

66.7% of the patients presented with chest pain, 16.2% with shortness of breath, 7.9% with exercise intolerance, and 9.2% with other complaints. 221 of the 229 patients (96.5%) had completed questionnaires, and their symptom category could be determined according to the 2019 ESC-CCS-GL [8]: 29.2% had typical, 41.6% atypical angina, and 29.2% non-anginal chest pain.

21.1% of the patients underwent NIGT, 17.1% an exercise-ECG and 92.5% an echocardiography at rest. If NIGT was performed, it was done by stress-echocardiography, myocardial perfusion scintigraphy, coronary CT-angiography and cardiac stress-MRI in 8.3% (4/48), 33.3% (16/48), 41.7% (20/48), 20.8% (10/48), respectively (with two patients undergoing coronary CT-angiography with consecutive stress-echocardiography). Results were considered pathological (signs of ischemia or > 50% stenoses) in 58.3% (28/48), inconclusive in 29.2% (14/48) and negative in 12.5% (6/48).

The CA diagnosed a CAD in 61,8% (141/228) of cases, with a 1-, 2- and 3-vessel disease in 24.8% (35/141), 24.8% (35/141) and 50.4% (71/141), respectively. Of the patients with 3-vessel disease 25.4% (18/71) had a diabetes. Additional invasive hemodynamic testing (e.g. fractional flow reserve (FFR)) was performed in 7.0% of cases and the patients underwent revascularization in 34.6% of cases (with PCI in 96.0% of cases (76/79)). In the GL-adherent group the CA was more likely to result in revascularization (44.5% vs. 17.1%, p < 0.001) (see Table 3 for details).

In regard to the safety of CA, there were no periprocedural deaths, myocardial infarctions, strokes or clinically relevant access site complications.

3.3. Guideline adherence of coronary angiography

According to the 2015 ESC-ACS-GL, the CAs were GL-adherent in 64.0% of cases (146/228). Adherence was determined by the presence of at least one IRC in 57.0% of cases (130/228), and based on prior NIGT in 7.0% of cases (16/228). None of the patients' medical records included documentation of a GRACE Score. 21.5% (28/130) of all the

Table 2
Baseline Characteristics of Patients in Total and with Guideline-Adherent and Non-Guideline -Adherent Coronary Angiography (n = 229). Baseline Characteristics of patients in total and with guideline-adherent and non-guideline-adherent coronary angiography in accordance with the 2015 European Society of Cardiology guidelines for the management of acute coronary syndromes without persistent ST-segment elevation.[5] If numbers do not equal the total number of patients, this is due to missing data. *Intermediate Risk Criterion defining guideline adherence of coronary angiography; **Defined as an estimated glomerular filtration rate < 60 ml/min/1.72 m^2. BMI – Body Mass Index; CABG – Coronary Artery Bypass Grafting, CAD – Coronary Artery Disease, PCI – Percutaneous Coronary Intervention.

Parameter	Statistic	Total	Guideline-Adherent* Coronary Angiography	Non-Guideline-Adherent* Coronary Angiography	p-value
Total	n	229			
Guideline Adherence determined	n/N (%)	228/229 (99.6)	146/228 (64.0)	82/228 (36.0)	
Age (years)	Mean (SD)	66.3 (10.5)	66.71 (10.5)	65.67 (10.6)	0.478
Gender male	n/N (%)	143/228 (62.7)	102/146 (69.9)	41/82 (50.0)	0.005
BMI kg/m^2	Mean (SD)	29.1 (5.9)	29.3 (6.0)	28.8 (5.7)	0.528
Cardiovascular Risk Factors					
Arterial Hypertension	n/N (%)	192/227 (84.6)	126/146 (86.3)	66/81 (81.5)	0.440
Hypercholesterolemia/dyslipidemia	n/N (%)	124/221 (56.1)	85/142 (59.9)	39/79 (49.4)	0.172
Diabetes mellitus*					<0.001
Type I	n/N (%)	2/228 (0.9)	2/146 (1.4)	0/82 (0.0)	
Type II	n/N (%)	70/228 (30.7)	70/146 (47.9)	0/82 (0.0)	
Current smoker	n/N (%)	77/226 (34.1)	49/145 (33.8)	28/81 (34.6)	0.382
Family history of CAD	n/N (%)	67/191 (35.1)	46/121 (38.0)	21/70 (30.0)	0.336
Cardiac History					
Prior myocardial infarction*	n/N (%)	45/227 (19.8)	45/146 (30.8)	0/81 (0.0)	<0.001
<3 months		3/45 (6.7)	3/45 (6.7)		
>3 months		42/45 (93.3)	42/45 (93.3)		
Prior PCI*	n/N (%)	89/228 (39.0)	89/146 (61.0)	0/82 (0)	<0.001
Prior CABG*	n/N (%)	18/228 (7.9)	18/146 (12.3)	0/82 (0)	0.002
Atrial fibrillation	n/N (%)	45/228 (19.7)	32/146 (21.9)	13/82 (15.9)	0.352
Non-cardiac Medical History					
Chronic obstructive lung disease	n/N (%)	33/228 (14.5)	19/146 (13.0)	14/82 (17.1)	0.522
Chronic renal insufficiency**	n/N (%)	15/228 (6.6)	15/146 (10.3)	0/82 (0)	0.006
Stroke	n/N (%)	19/228 (8.3)	15/146 (10.3)	4/82 (4.9)	0.244
Peripheral/vascular disease	n/N (%)	23/228 (10.1)	17/146 (11.6)	6/82 (7.3)	0.417
Referred by					0.306
Family doctor	n/N (%)	75/223 (33.6)	48/142 (33.8)	27/81 (33.3)	
Self-presentation	n/N (%)	55/223 (24.7)	37/142 (26.1)	18/81 (22.2)	
Self-presentation by emergency services	n/N (%)	51/223 (22.9)	35/142 (24.6)	16/81 (19.8)	
Specialist (cardiology)	n/N (%)	26/223 (11.7)	16/142 (11.3)	10/81 (12.3)	
Other	n/N (%)	16/223 (7.2)	6/142 (4.2)	10/81 (12.3)	

patients with at least one IRC underwent additional NIGT prior to their CA; 20.4% (20/98) of all the other patients (i.e. those without IRC) received NIGT. In the multivariate analysis, there were no factors significantly associated with the GL-adherent use of CA.

Using the definitions of the 2020 ESC-ACS-GL with complete data for 221 of the 229 patients, GL adherence with regard to the use of CA was 20.4% (45/221) (see Fig. 1 for details). PTP was 23.7 ± 12.6%, with no significant difference between GL-adherent and non-adherent CAs (PTP 24.0% vs. 23.6%, p = 0.840). In GL-adherent patients, i.e. those with prior NIGT with at least an inconclusive finding, the CA resulted in revascularization significantly more often than in the non-adherent group (51.1% (23/45) vs. 30.1% (53/176), p = 0.013).

4. Discussion

4.1. Discussion

This is the first German multicenter study to assess the degree of GL adherence in the use of CA on patients who present at the ED with symptoms potentially attributable to myocardial ischemia but no AMI. According to the 2015 ESC-ACS-GL, the use of CA was GL-adherent in 64.0% of cases. If the 2020 ESC-ACS GL had been applied, which recommend a non-invasive, image-guided approach in this population, the GL-adherence rate would have dropped to 20.4%. Implementing these guideline recommendations would require a fundamental shift from an invasive CA-based strategy to a primarily non-invasive diagnostic approach.

The inclusion criteria for our study population mirror those of the German national quality assurance cohort of patients undergoing CA with suspected “ACS without myocardial infarction”, which represents at least 10% of the annual CA and PCI volume in Germany [10]. The populations are comparable in regard to age (66.3 vs. 68.5 years), female gender (36.7 vs. 36.1%), and body mass index (29.1 vs. 28.2 kg/m^2) [10]. The importance of clear GL recommendations in ensuring a resource-efficient diagnostic work-up for patients presenting at the emergency-department with suspected myocardial ischemia, is underlined by the findings of the Dutch HEART score validation cohort: the vast majority (93.5%) of such patients does not have an AMI [19].

Our study population was recruited across seven centers in North Rhine Westphalia and Hamburg, all of which were non-university hospitals that provide 24/7 CA services for patients with AMIs. In Germany, CAs are conducted by 813 hospitals (43 university and 770 non-university hospitals), with a median annual volume in the range of 1000 to 1499 CAs [10,20]. With 830 to 4500 CAs per year (median: 1330), the participating study centers reflect a representative spectrum of the hospitals that perform CAs, at least in terms of annual volumes. Furthermore, 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 [21].

According to the 2015 ESC-ACS GL, the use of CA was GL-adherent in 64.0% (146/228) of patients in the study cohort. In the majority of patients with GL-adherent use of CA, adherence was determined by the

Table 3
Patients' Main Complaints, Angina Pectoris Category, Diagnostic Work-Up and Resulting Revascularization in Total and in Patients with Guideline-Adherent and Non-Guideline-Adherent Coronary Angiography. Patients' main complaints, angina pectoris category, diagnostic work-up and resulting revascularization in total and in patients with guideline-adherent and non-guideline-adherent coronary angiography in accordance with the 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation.[5] * Based on the patient questionnaire. CABG – Coronary Artery Bypass Grafting, PCI – Percutaneous Coronary Intervention, SPECT - Single Photon Emission Computed Tomography.

Parameter	Statistic	Total	Guideline-Adherent Coronary Angiography	Non-Guideline-Adherent Coronary Angiography	p-value
Main Complaint*					
Chest pain	n/N (%)	152/228 (66.7)	102/146 (69.9)	50/82 (61.0)	0.539
Shortness of breath	n/N (%)	37/228 (16.2)	20/146 (13.7)	17/82 (20.7)	
Exercise intolerance	n/N (%)	18/228 (7.9)	10/146 (6.8)	8/82 (9.8)	
Other complaints	n/N (%)	21/228 (9.2)	14/146 (9.6)	7/82 (8.5)	
Angina Pectoris*					
Typical angina	n/N (%)	66/226 (29.2)	42/144 (29.2)	24/82 (29.3)	0.813
Atypical angina	n/N (%)	94/226 (41.6)	58/144 (40.3)	36/82 (43.9)	
Non-Anginal Chest Pain	n/N (%)	66/226 (29.2)	44/144 (30.6)	22/82 (26.8)	
Non-Invasive Testing					
Non-invasive image guided testing	n/N (%)	48/228 (21.1)	44/146 (30.1)	4/82 (4.9)	<0.001
Stress echocardiography	n/N (%)	4/228 (1.8)	4/146 (2.7)	0/82 (0)	0.324
Cardiac stress magnet resonance imaging	n/N (%)	10/228 (4.4)	9/146 (6.2)	1/82 (1.2)	0.158
Myocardial perfusion SPECT	n/N (%)	16/228 (7.0)	13/146 (8.9)	3/82 (3.7)	0.223
Coronary CT angiography	n/N (%)	20/228 (8.8)	20/146 (13.7)	0/82 (0)	0.001
Coronary Angiography					
Coronary artery disease	n/N (%)	141/228 (61.8)	117/146 (80.1)	24/82 (29.3)	<0.001
1- vessel disease	n/N (%)	35/141 (24.8)	9/35 (25.7)	26/35 (74.2)	n.a.
2- vessel disease	n/N (%)	35/141 (24.8)	8/35 (22.9)	27/35 (77.1)	
3- vessel disease	n/N (%)	71/141 (50.4)	18/71 (25.4)	53/71 (74.6)	
Fractional flow reserve	n/N (%)	16/228 (7.0)	10/146 (6.8)	6 (7.3)	0.611
Revascularization	n/N (%)	79/228 (34.6)	65/146 (44.5)	14/82 (17.1)	<0.001
PCI	n/N (%)	76/228 (33.3)	114/146 (78.1)	13/82 (15.9)	
CABG	n/N (%)	3/228 (1.3)	2/146 (1.4)	1/82 (1.2)	

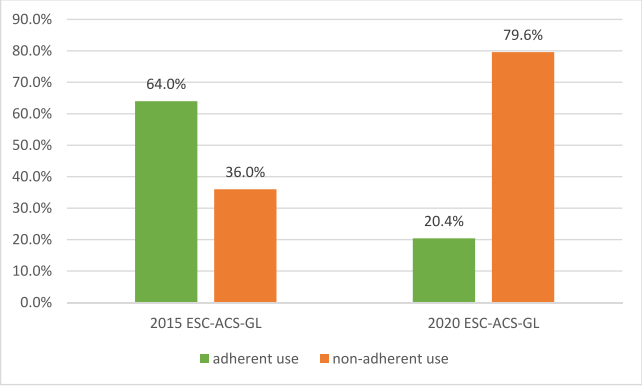

Fig. 1. Rates of guideline-adherent or non-adherent use of coronary angiography according to the 2015 and 2020 European Society of Cardiology guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation (ESC ACS GL), respectively.

presence of at least one IRC (i.e. in 89%, or 130/146 patients). The remaining 11% (16/146 patients) underwent CA following pathological, or at least inconclusive, NIGT. Since the 2020 ESC-ACS-GL recommendations endorsed a NIGT-based strategy as outlined in the 2019 ESC-CCS-GL, this would have reduced GL adherence to 20.4% [6,8]. The just published 2023 ESC-ACS-GL put even more priority on the use of coronary CT-angiography or the other NIGT modalities in the study population [9]. Applying the selective invasive approach outlined in these GL, the GL-adherence rate in the use of CA would remain at 20.4%. In regard to improve GL adherence in the (over-) use of CA in Germany, the current availability of NIGT capacities would need to be significantly increased. Especially difficulties in access is considered a major barrier in the use of the NIGT modalities [14]. In addition to preventing unnecessary invasive CAs and reducing health care expenditures [12],

Table A1
Definition of very high, high, intermediate and low risk categories and the recommended diagnostic approach according to the 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation.[5] CABG – Coronary Artery Bypass Grafting, eGFR – estimated glomerular filtration rate, GRACE-Score - Global Registry of Acute Coronary Events 2.0 Score, LVEF – left ventricular ejection fraction, PCI – percutaneous coronary intervention.

Risk category	Risk criteria	Recommended Approach
Very-High Risk Criteria	· Haemodynamic instability or cardiogenic shock · Recurrent or ongoing chest pain refractory to medical treatment · Life-threatening arrhythmias or cardiac arrest · Mechanical complications of myocardial infarction · Acute heart failure · Recurrent dynamic ST- or T-wave changes, particularly with intermittent ST-elevation	Immediate (<2 h) coronary angiography
High Risk Criteria	· Rise of fall in cardiac troponin compatible with myocardial infarction · Dynamic ST- or T-wave changes (symptomatic or silent) · GRACE-Score > 140	Early (<24 h) coronary angiography
Intermediate Risk Criteria	· Diabetes mellitus · Renal insufficiency (eGFR < 60 ml/min/1.73 m^2) · LVEF < 40% or congestive heart failure · Early post-infarction angina · Prior PCI · Prior CABG · GRACE risk score > 109 and < 140	Selective (<72 h) coronary angiography
Low risk criteria	· Any characteristic not mentioned above	Non-invasive testing

Table A2
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.[8.]

	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%

extending the use of NIGT could also lead to further benefits for patients: As outlined by Weir-McCall et al., an increased use of coronary CT-angiography did not increase the overall volume of CA, but appeared to result in a population-wide reduction of cardiovascular mortality (at least in a National Health Service setting in the United Kingdom) [22].

In order to stimulate the utilization of NIGT in the German health care system, reimbursement patterns should be adopted. The following facts provide potential starting points: (1) coronary CT-angiography and stress cardiac MRI are not reimbursed in the outpatient setting; (2) in-hospital NIGT does not trigger a higher reimbursement than resting echocardiography alone; (3) in fact, only the use of invasive CA leads to a higher reimbursement (see appendix chapter 11.3 for details).

In our study, 34.6% of the cases resulted in revascularization by PCI or CABG. Applying the 2020 ESC-ACS-GL the revascularization rate in the GL-adherent group (i.e. with preceding NIGT and therefore objective signs of ischemia) was 51.1%, whereas in the non-adherent group (i.e. patients with direct CA without objective signs of ischemia) it was 30.1%. Our data, which showed a high revascularization rate among patients with no objective signs of ischemia, may also indicate a significant rate of inappropriate revascularizations, as hypothesized for the German healthcare setting by Figulla et al [2]. Based on data obtained from the US national cardiovascular registry, Bradley et al. emphasized the importance of an appropriate selection of patients for invasive CA, as inappropriate CA would lead to inappropriate revascularizations [23]. This further underlines the need for the stimulation of an increased utilization of NIGT in the German healthcare setting.

4.2. Limitations

First, the expected 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 uncompetitive with industry-sponsored trials, (3) of 35 addressed study-centers 26 declined participation due to financial reasons but also mentioned concerns regarding the participation of SHI companies and (5) due to funding restraints, the recruitment period could not be extended beyond 32 months. However, due to the observational nature of the study, the number of 229 patients in this cohort appeared to be sufficient for assessing the degree of GL adherence.

Secondly, in order to enable the collection of health claims data on a patient level as intended by the study design, only patients who were insured by the two collaborating SHI companies were recruited. However, as these companies represented about one third of patients at the recruiting centers, the results should be generalizable to the 90% of German citizens who are insured via the SHI system [24].

Thirdly, the patient questionnaire and the evaluating rules used to determine the patients' main complaints were not independently validated [11]. However, the patient questionnaire, which was completed by the patients alone, and collected by study personnel, allowed data on the patients' main complaints to be collected with a reduced risk of physician bias.

Finally, the calculation of the GRACE Score is recommended by the 2015 ESC-ACS-GL, with a GRACE-Score of 110–139 being an additional IRC [7]. As GRACE Scores were not documented in the health records in any of the recruited patients, GL adherence may have been underestimated, at least for the 2015 ESC-ACS-GL.

4.3. Conclusion

In conclusion, this is the first prospective multicenter German study to evaluate the degree of GL adherence in the use of CA in the population of patients who present at the ED without an AMI. The use of CA in this population was adherent to the 2015 ESC-ACS-GL in the majority of cases. Applying the 2020 ESC-ACS-GL, the degree of GL-adherence would have dropped markedly from 64% to 20%.

Adherence to the 2020 ESC-ACS-GL would result in the highest revascularization rate with preceding objective signs of ischemia, and is associated with the most appropriate use of CA and subsequent revascularization. In situations where NIGT capacity is limited but CA services are available, the selective invasive approach outlined in the 2015 ESC-ACS-GL (i.e. diagnostic CA for patients with at least one IRC and NIGT for those with no IRC) may be an acceptable compromise. Altogether, in order to ensure that patients for invasive CAs are selected appropriately, it is essential to expand the utilization of NIGT by increasing testing capacities and enabling timely in- or outpatient access for emergency department patients.

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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. German Version (Original)

Sehr geehrte Studienteilnehmer,

mit diesem Fragebogen möchten wir gerne von Ihnen erfahren, welche Beschwerden Sie zu uns geführt haben und wie Sie diese einschätzen. Um Ihre Antworten mit denen anderer Teilnehmer vergleichen zu können, wenden wir uns an Sie mit einem standardisierten Fragebogen mit größtenteils vorgegebenen Antwortmöglichkeiten.

Kreuzen sie bitte jeweils das für Sie zutreffende an:

1. Beschwerdesymptomatik

Hierbei möchten wir sie zu ihren Hauptbeschwerden aus kardiologischer Sicht befragen.

1.1. Was ist ihre Hauptbeschwerde, weswegen sie sich bei uns vorstellen (*eine Antwort*)?

Beschwerden im Brustbereich	☐
Beschwerden außerhalb des Brustbereiches	☐
Kurzatmigkeit	☐
Verminderte körperliche Leistungsfähigkeit	☐
Herzklopfen	☐
Übelkeit	☐
Andere Beschwerden	☐
falls andere Beschwerden, welche:_____	

1.2 Wo sind die Beschwerden?

Benennen sie bitte den Ort/die Orte, bzw. den Bereich/die Bereiche an dem/denen die Beschwerden typischerweise auftreten (*mehrere Antworten möglich*)

Nacken	☐			
Rücken	☐			
Kiefer	☐			
Schulter	Rechts ☐	Links	☐	Beidseits ☐
Arm	Rechts ☐	Links	☐	Beidseits ☐
Brustkorb	☐			
Rechts ☐	Mitte	☐	Links ☐	
Hinter dem Brustbein	☐			
Oberbauch	☐			
Rechts ☐	Links	☐	Beidseits ☐	
Lokalisation nicht klar zu lokalisieren	☐			

1.3 Wie würden sie die Beschwerden am ehesten beschreiben?

1.3.1 Wie ist der Schmerzcharakter? (*eine Antwort*)

Druck (dumpf, stumpf)	☐
Stechen (scharf, spitz)	☐
Klemmen, Einengung	☐
Brennen	☐
Unspezifisch	☐
Keine Angabe möglich	☐

1.3.2. Wie groß ist der Schmerzbereich? (*eine Antwort*)

Eher punktförmig (<2€ Münze)	☐
Eher flächig (>2€ Münze)	☐
Keine Angabe möglich	☐

1.3.3. In welchen situationen treten die Beschwerden typischerweise auf? (*Mehrfachnennung möglich*)

Bei körperlicher Belastung	☐
Auf Druck auslösbar	☐
Durch bestimmte Bewegungen auslösbar	☐
Atemabhängig oder bei Husten	☐
Aus der Ruhe heraus	☐
Bei emotionaler Belastung	☐
Nachts im Liegen	☐
Andere Situation:_____	

1.4 Wie ist der verlauf des Schmerzes/ der Beschwerden?

1.4.1 Wie beginnt der Schmerz/ die Beschwerde? (*eine Antwort*)

Plötzlich/Schlagartig	☐
Anstieg über Minuten	☐

1.4.2. Wie lange dauert typischerweise eine Schmerz-/ Beschwerdeepisode? (*eine Antwort*)

Sekunden	☐
1–30 Minuten	☐
>30 Minuten	☐

1.4.3. Durch was lassen sich die Beschwerden lindern? (*eine Antwort*)

Einnahme von Nitroglyzerin	☐
Anhalten/ Pause machen	☐
Anderes	☐
Falls anderes, bitte nennen:_____	

1.4.4. Wie häufig haben sie im schnitt eine Schmerz-/ Beschwerdeepisode? (*eine Antwort*)

Mehrmals täglich	☐
Einmal am Tag	☐
Mehrmals pro Woche	☐
Einmal pro Woche	☐
Weniger als einmal pro Woche	☐
Einmaliges Ereignis	☐

1.4.5. Seit wann haben sie die Beschwerden? (*eine Antwort*)

Weniger als 1 Woche	☐
Seit 1–2 Wochen	☐
Seit 2–4 Wochen	☐
Seit 4–8 Wochen	☐
Seit > 8 Wochen bis 6 Monate	☐
Seit 6–12 Monaten	☐
Seit > 12 Monaten	☐

1.4.6. Ihrer ansicht nach werden die Beschwerden verursacht durch? (*eine Antwort*)

das Herz	☐
Muskeln oder Skelettsystem (Knochen)	☐
Magen oder Darm	☐
die Lunge	☐
andere Faktoren	☐
falls andere, bitte nennen_____	

2. Körperliche Leistungsfähigkeit

Im Folgenden Abschnitt werden wir ihnen einige Fragen stellen, um ihre körperliche Leistungsfähigkeit und damit den Schweregrad der Beschwerden beurteilen zu können.

Bitte wählen Sie aus den untenstehenden Aussagen, die auf Sie am ehesten zutreffende aus:

☐	Selbst bei stärkster körperlicher Anstrengung treten keine Beschwerden auf.
☐	Keine Beschwerden bei normaler körperlicher Betätigung, wie schnelles Gehen in der Ebene oder Treppensteigen. Beschwerden treten aber bei starker oder plötzlicher Belastung auf.
☐	Beschwerden bei normaler Belastung im Alltag wie schnelles Gehen, Bergaufgehen, emotionalem Stress oder bei Belastung nach einer Mahlzeit, bzw. bei kalten Temperaturen. Die Beschwerden beginnen aber z.B. erst nach mehr als 400–500 m schnellem Gehen oder mehr als 1 Etage Treppensteigen.
☐	Beschwerden bei leichter körperlicher Anstrengung, wie z.B. Gehen von weniger als 400–500 m oder schon während einer Etage Treppensteigen.
☐	Beschwerden treten bei der geringsten körperlichen Betätigung auf (z.B. wenige Schritte in der Wohnung).

A.1.3. 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. 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	☐				

2. How would you most likely describe the discomfort?

2.1. What is the nature of pain?

Pressure (dull)	☐
Stinging pain (sharp, pointed)	☐
Constricting, strangling	☐
Burning	☐
Unspecific	☐
No specification possible	☐

2.2. How large is the area of pain?

Rather punctiform (<2€ coin)	☐
Rather areal (>2€ coin)	☐
No specification possible	☐

2.3. 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:_____	

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

3.1. How does the pain/ discomfort begin?

Suddenly/ abruptly	☐
Increases over minutes	☐

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

Seconds	☐
1–30 min	☐
>30 min	☐

3.3. What relieves the discomfort?

Taking nitroglycerin	☐
Resting	☐
Other	☐
Other:_____	

3.4. 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	☐

3.5. How long have you had these complaints?

For<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	☐

3.6. 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>400–500 m of walking fast or after climbing more than one flight of ordinary stairs.
☐	Complaints during mild exertion such as walking<400–500 m or climbing one flight of stairs.
☐	Complaints occur with the slightest physical activity (e.g., a few steps in the apartment).

A.1.4. Evaluating rules to define the type of chest pain

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.

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

1. 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.2. Appendix tables

Table A1 – Definition of very high, high and intermediate risk criteria
Table A2 – 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.

A.3. Details on reimbursement patterns of non-invasive and invasive testing for myocardial ischemia in the German health care setting

German DRG System 2022 (G-DRG 2022):
Assumptions:

- Diagnosis Unstable Angina (ICD-Code I20.0), length of stay 2 days.
- Testing: coronary CT-angiography (OPS-code 3–224.3), stress echocardiography (OPS-code 3–031), myocardial perfusion scintigraphy (OPS-code 3–721.21), stress cardiac magnetic resonance imaging (OPS-code 3–824.2), diagnostic coronary angiography (OPS-code 1–275.0).
- German-wide case value 3.833.07 €.
- DRG web-grouper: https://www.drg-research-group.de.

Result:

- Non-invasive image guided testing triggers the DRG F72B (case weight 0.367).
- Invasive coronary angiography triggers the DRG F49G (case weight 0.548).
- Higher reimbursement of 693.79€ for CA in contrast to no testing or NIGT.

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