Aus dem

Fachbereich Health Services Management, Fakultät für Betriebswirtschaft,

Ludwig-Maximilians-Universität

Guideline-recommended care for coronary heart disease in Germany: A regional analysis based on routine data of the statutory health insurance

Dissertation
zum Erwerb des Doctor of Philosophy (Ph.D.)
an der Medizinischen Fakultät der
Ludwig-Maximilians-Universität München

vorgelegt von

Julia Anna-Maria Sylvia
Frank-Tewaag

aus
München

Jahr
2024

Mit Genehmigung der Medizinischen Fakultät der
Ludwig-Maximilians-Universität München

Erstes Gutachten:	Prof. Dr. Leonie Sundmacher
Zweites Gutachten:	Prof. Dr. Eva Grill
Drittes Gutachten:	Priv. Doz. Dr. Thomas Stocker
Viertes Gutachten:	Prof. Dr. Hans Theiss

Dekan:	Prof. Dr. med. Thomas Gudermann

Tag der mündlichen Prüfung:	23.04.2024

Affidavit

LMU | LUDWIG-MAXIMILIANS-UNIVERSITÄT MÜNCHEN | Promotionsbüro Medizinische Fakultät | MMRS

Affidavit

Frank-Tewaag, Julia

Surname, first name

TU München, Georg-Brauchle-Ring 60/62

Street

80992 München

Zip code, town, country

I hereby declare, that the submitted thesis entitled:

Guideline-recommended care for coronary heart disease in Germany: A regional analysis based on routine data of the statutory health insurance

is my own work. I have only used the sources indicated and have not made unauthorised use of services of a third party. Where the work of others has been quoted or reproduced, the source is always given.

I further declare that the dissertation presented here has not been submitted in the same or similar form to any other institution for the purpose of obtaining an academic degree.

München, 23.05.2024

place, date

Julia Frank-Tewaag

Signature doctoral candidate

Confirmation of congruency

LMU | LUDWIG-MAXIMILIANS-UNIVERSITÄT MÜNCHEN | Promotionsbüro Medizinische Fakultät | MMRS

Confirmation of congruency between printed and electronic version of the doctoral thesis

Frank-Tewaag, Julia
____
Surname, first name

TU München, Georg-Brauchle-Ring 60/62
____
Street

80992 München
____
Zip code, town, country

I hereby declare, that the submitted thesis entitled:

Guideline-recommended care for coronary heart disease in Germany: A regional analysis based on routine data of the statutory health insurance

is congruent with the printed version both in content and format.

München, 23.05.2024
____
place, date

___________Julia Frank-Tewaag______
Signature doctoral candidate

Table of content

Affidavit 3

Confirmation of congruency 4

Table of content 5

List of abbreviations 6

List of publications 7

Your contribution to the publications 8

1.1 Contribution to paper 1 8

1.2 Contribution to paper 2 8

2. Introductory summary 9

2.1 Background 9

2.2 Aim 10

2.3 Method 11

2.3.1 Systematization of guideline recommendations and the depiction in GKV routine data 11

2.4 Summary of results and scientific contribution 14

2.4.1 Paper 1 14

2.4.2 Paper 2 14

2.5 Strength and limitations 15

2.6 Conclusion and outlook 17

3. Paper 1 19

4. Paper 2 36

References 52

Acknowledgements 55

List of all scientific publications 56

List of abbreviations

ÄQZ Ärztliches Zentrum für Qualität in der Medizin

ASA acetylsalicylic acid

ATC Anatomical Therapeutic Chemical

BÄK Bundesärztekammer

COV coefficient of variation

DMP disease management program

EBM Einheitlicher Bewertungsmaßstab (Uniform Value Scale)

GISD German Index of Social Deprivation

GKV Gesetzliche Krankenversicherung (statutory health insurance)

ICD-10 International Statistical Classification of Diseases and Related Health Problems, 10th version

KBV Kassenärztliche Bundesvereinigung (National Association of Statutory Health Insurance Physicians)

OPS Operationen- und Prozedurenschlüssel (Operation and Procedure Code)

SCV systematic component of variation

SSA state-sequence-analysis

List of publications

Title	Authors	Year	Journal	Rank of Publication	Reference
Regional variation in coronary angiography rates: the association with supply factors and the role of indication: a spatial analysis	Julia Frank-Tewaag Julian Bleek Christian Günster Udo Schneider Dirk Horenkamp-Sonntag Ursula Marschall Sebastian Franke Kathrin Schlößler Norbert Donner-Banzhoff Leonie Sundmacher	2022	BMC Cardiovascular Disorders	101/143	(1)
Use of guideline-recommended drug therapy in patients undergoing percutaneous coronary intervention for stable coronary heart disease in Germany: a multilevel analysis of nationwide routine data	Julia Frank-Tewaag Julian Bleek Dirk Horenkamp-Sonntag Ursula Marschall Uwe Zeymer Norbert Donner-Banzhoff Leonie Sundmacher	2020	BMJ Open	64/167	(2)

Your contribution to the publications

1.1 Contribution to paper 1

Contribution of PhD candidate	Contribution of co-authors
Conceptualization, Methodology, Data curation, Formal analysis, Validation, Visualization, Writing- Original draft preparation; (50 %)	JB: Conceptualization, Data curation, Writing—review and editing; (4 %)
	CG: Conceptualization, Writing—review & editing; (1%)
	US: Conceptualization, Data curation, Writing—review and editing (4 %)
	DHS: Conceptualization, Data curation, Writing—review and editing (4 %)
	UM : Conceptualization, Data curation, Writing—review and editing (4 %)
	SF: Data curation, Writing—review and editing (2 %)
	KS: Conceptualization, Project administration, Writing—review and editing; (1 %)
	NDB: Conceptualization, Funding acquisition, Writing—review and editing; (10 %)
	LS: Conceptualization, Funding acquisition, Methodology, Supervision, Validation Writing—review and editing (20 %)

1.2 Contribution to paper 2

Contribution of PhD candidate	Contribution of co-authors
Conceptualization, Methodology, Data curation, Formal analysis, Validation, Visualization, Writing- Original draft preparation; (60 %)	JB: Conceptualization, Data curation, Writing—review and editing; (4 %)
	DHS: Conceptualization, Data curation, Writing—review and editing (4 %)
	UM : Conceptualization, Data curation, Writing—review and editing (4 %)
	UZ: Conceptualization, Writing—review and editing (3 %)
	NDB: Conceptualization, Funding acquisition, Writing—review and editing; (5 %)
	LS: Conceptualization, Funding acquisition, Methodology, Supervision, Validation Writing—review and editing (20 %)

2. Introductory summary

2.1 Background

In view of the rapid development of new medical technologies and the increasing flood of information, medical guidelines can offer orientation and impart the best available evidence in everyday care. By definition of the Ärztliches Zentrum für Qualität in der Medizin (ÄQZ), the Bundesärztekammer (BÄK) and the Kassenärztliche Bundesvereinigung (KBV), medical guidelines are 'systematically developed, scientifically founded and practice-oriented decision-making aids for the appropriate medical conduct for specific health problems. They deliver the consensus of several experts from different specialist areas and working groups that has been achieved according to a defined, transparent procedure for a specific medical approach' (3). They are intended to promote the transparency of medical decisions, the quality of medical care and good medical practice, taking into account the available resources of the health system (3). Guidelines provide boundaries for decision-making. The appropriateness of specific recommendations must always be assessed in the individual case, considering the existing circumstances of each situation. From guidelines that meet the essential methodological requirements, indicators can be derived that can be used to quantify the volume and quality of medical care and to distinguish areas with sound practice and those in need of improvement. Such guideline-based indicators are an essential tool for the evaluation of health services and outcomes in everyday medical practice. The information obtained thereby can, for example, support needs-based care planning as well as economic and social allocation decisions.

Depending on the clinical situation, the quality of the available evidence and the precision of the recommendations must be taken into account. In the case of some decisions, such as those without a clear recommendation or in which soft criteria are applied, there is room for discretion as to how to proceed. Wennberg et al. (4) suggest that there is a relationship between the availability as well as the quality of evidence in favour of a specific treatment and the variation in its utilization. Consequently, deviation resulting in greater variation are more likely to occur when there is lower certainty about the basis of evidence for a treatment option. The concept relies on the assumption that providers intent to maximize the perceived health of their patient but may deviate from this aim, because of other factors such as ethical considerations, financial incentives, resource capacity and patient demand (5). Health care is divided into three categories according to the differentiation by Wennberg et al (4). Effective care involves treatment strategies with clear benefits supported by a firmly grounded evidence base. Preference-sensitive occurs when suitable alternatives are available, and the choice requires a compromise as the risks and benefits of the options must be weighed. One speaks of supply-sensitive care when, the lack of recommendations and evidence on tried-and-tested treatment strategies leaves a wider scope for decision-making or when there is greater medical uncertainty (4, 5).

This PhD project focuses on patients with coronary heart diseases. Cardiovascular diseases, including coronary heart disease, are among the most common causes of death and disability in Germany and other industrialized countries (6, 7). Owing to the high medical, but also health-economic, relevance of this widespread disease, the best possible diagnosis and therapy are required. The national care guide and international guidelines detail comprehensive recommendations for anamnesis, diagnosis, and treatment of the disease. The procedures that are at the centre of the two analyses, coronary angiography and percutaneous coronary intervention, were selected because, they are one of the most frequently performed diagnostic procedures in hospitals in Germany (8) and considerable regional variation in the rates of coronary angiography and percutaneous coronary intervention have been reported (9-12). Furthermore, in comparison with the rates exhibited in other European health systems, the rates of coronary angiography and percutaneous coronary intervention in Germany have been regarded to be rather high (9). Whether these findings actually reflect differences in medical needs or not, has therefore been discussed repeatedly (9-11).

Coronary angiography is an invasive diagnostic procedure to investigate the morphology of the blood vessels of the heart. Depending on its results, a decision between a revascularization, namely percutaneous coronary intervention and coronary artery bypass graft surgery, or conservative treatment only can be made. The importance of coronary angiography in the preparation of subsequent treatment is emphasised in the guidelines, while solely diagnostic indications are restricted (13-17). That is why, in the case of these procedures, the assessment of the indication according to guideline recommendations is of special interest. Drug therapy has come to be one of the cornerstones of secondary prevention in patients with stable coronary heart disease. The clinical guidelines for coronary heart disease recommend drug therapy as the first means of treatment for stable coronary heart disease, while the indication for percutaneous coronary intervention is limited to patients with persistent symptoms even with optimal medical therapy (13-15, 17).

Both papers are based on a nationwide data set statutory health insurer providers (1, 2). Routine data from the statutory health insurance providers (GKV routine data) are a special type of secondary data and are primarily collected for billing purposes and for reimbursement of costs but may also be used for research purposes. GKV routine data are generated under everyday conditions and thus depict the current care situation, which is why they are increasingly being used as a data source in the context of health services research. On account of their extensive size, GKV routine data also offer the possibility of regional evaluations on a national level. In this way, questions about the regional quality of care on the basis of evidence-based care guidelines can be addressed and possible regional differences can be compared. The results of such analyses can be a starting point for targeted regional studies and structural development, and for reducing under-, over- and incorrect provision of care (18-20). In particular, the analyses can also give indications of the determinants of utilization at the supply level, i.e., provide indications of supply-sensitive provision of care, for example.

2.2 Aim

The aim of this PhD project was to investigate the use of health services in accordance with guideline recommendations and to examine regional practice variation based on GKV routine data from statutory health insurance providers in Germany. First, the extent to which recommendations from the national and European guidelines for the treatment of coronary heart disease can be examined using GKV routine data was assessed. Second, it was examined whether selected recommendations from guidelines for coronary heart disease are reflected in the clinical practice based on a nationwide GKV routine data set. Lastly, it was assessed whether there are indications that the recommendations are adhered to in varying degrees and if these differences are associated with various characteristics including regional health care supply. This was done using two articles (1, 2) focusing on different guideline recommendations in the context of coronary angiography and percutaneous coronary intervention. Both papers draw upon on a nationwide GKV routine data set from three statutory health insurance providers (1, 2). GKV routine data offer a number of advantages that make it an attractive data basis for the analysis of current medical care, but they also have some important limitations. These were discussed in the course of the PhD project. Although both analyses take regional aspects into account, they use different perspectives. The first focused on a spatial analysis at the regional level and the second on a multi-level analysis that takes into account both the individual patient and the regional perspective.

Paper 1 (1) focused on the use of coronary angiography. This procedure is well suited for examining variations in medical practice because the available evidence and appropriateness criteria allow discretion in some patient groups and the procedure shows considerable heterogeneity in its benefits across patient populations. Therefore, the role of the indication for the procedure and its relationship with respect to the association of its use with the regional capacity was examined. In Paper 1 (1), it is hypothesized that, due to the different degrees of certainty surrounding the treatment decision and differences concerning the expected benefit in the acute (cases with myocardial infarction) and non-acute situation (cases without myocardial infarction), the regional variation in rates and the association of supply and need differ according to the indication for coronary angiography (1). The regional variation in the rates of coronary angiography was investigated in small-area analyses at the level of the 401 districts. Lastly, the association between regional supply and the rates of the procedure were assessed, while controlling for need in spatial models (1).

The aim of Paper 2 (2) was to assess whether patients obtained optimal medical therapy prior to elective percutaneous coronary intervention in Germany. Because chest pain relief plays a central role in the therapy, particularly when considering percutaneous coronary intervention as a succeeding treatment, symptom-oriented therapy was assessed in an additional analysis (2). Both are an example of effective care. First, it was examined if the clinical practice mirrors the guidelines recommendations for secondary prevention in patients with stable coronary heart disease and whether there are opportunities to improve their care. Second, a multi-level model was then estimated to investigate the role of the characteristics of the patient and the regional availability of health services on the use of drug therapy (2).

A third paper, which is not part of the project, demonstrated further application of the systematization of guideline recommendations in GKV routine data to identify empirical ambulatory care sequences using data mining methods, in particular state-sequence analysis (SSA) (21).

2.3 Method

2.3.1 Systematization of guideline recommendations and the depiction in GKV routine data

Both papers were based on cohorts that stem from a comprehensive linked nationwide longitudinal GKV routine data set from three statutory health insurance providers for the years 2014–2016 (1, 2). The data encompass insured aged 18 years or older undergoing coronary angiography in the year 2016, including all of the patients' reimbursable hospital (inpatient and outpatient), office-based practice and prescription billing data between 2014 and 2017. The dataset also includes the related diagnoses and demographic information for the patient.

On account of their many advantages, GKV routine data are generally an attractive data source for investigating adherence to medical guidelines. The broad character of the database allows for consideration of the use of health services at the population level and across the course of care. However, several assumptions regarding the guideline, the indication and the data basis need to be met to be able to depict a given guideline recommendation with GKV routine data. The health care practice, in terms of diagnostics and therapy to be examined, should be coded using a standardized coding system such as Einheitlicher Bewertungsmaßstab (EBM), Operationen- und Prozedurenschlüssel (OPS), International Statistical Classification of Diseases and Related Health Problems, 10th version (ICD-10) and Anatomical Therapeutic Chemical (ATC) codes. Temporal and quantitative information should be specified in the coding in order to be able to map these recommendations as precisely as possible with the help of GKV routine data. Measures that are not relevant to billing are not coded and are therefore also not included in the GKV routine data. A differentiated comparison between guideline recommendations and the reality of care is also limited if the recommendations are not formulated precisely enough. However, the precision of the recommendations in the guidelines and the opportunity for discretionary judgement is an interesting subject for research in itself.

2.3.1.1 The indication of coronary angiography (Paper 1)

The high and widely varying rates of coronary angiography raise the question to what extent these are actually justified by medical need. As explained earlier, assessment of the indication for the procedures according to guideline recommendations is of special interest. The national treatment guideline recommends the use of the Marburger Herz Score and the pre-test probability for a stenosing coronary heart disease based on age, gender and the quality of chest pain to determine the further course of action (14, 15). Because some of the required clinical information, such as the quality of chest pain and other criteria for assessing stenosing coronary heart disease as the cause of chest pain, are not captured within the GKV routine data, the doctor's risk assessment cannot be mapped. However, the indication determined by the doctor in the treatment case of the procedure is captured in ICD-10 coding. This allowed an interesting insight into the indication assessment at a population level and a study of the regional variation in the rates of coronary angiography. As described earlier, the appropriateness criteria and evidence and in medical guidelines offer room for discretionary judgement according to the indication for the coronary angiography. In cases where symptoms suggest myocardial infarction (or acute coronary syndrome), the benefits of percutaneous coronary intervention are firmly established (22, 23). In the case of stable coronary heart disease, the decision is not so unequivocal (24, 25). The use of elective coronary angiography in these non-acute situations can be classified as preference sensitive as alternative options are available, and the treatment decision requires a risk-benefit assessment. Coronary angiographies carried out on in hospital (inpatient or outpatient) or in an office-based practice in 2016 and were identified by the procedure code and the coronary angiography cases were classified according to the relating diagnoses. This allowed the comparison of the coronary angiography rates in situations where there is greater uncertainty (cases without myocardial infarction) as opposed to the effective care situation (case with myocardial infarction), where the decisions undergo coronary angiography are guided by a strong evidence base (1). In a sensitivity analysis, coronary angiography rates of cases with acute coronary syndrome and cases without acute coronary syndrome and cases treated for stable coronary heart disease or chest pain were inspected. (1). The GKV routine data set was supplemented with data from other sources including additional GKV routine data, information regarding the regional social deprivation (26) and data detailing hospitals with cardiac catheterization facilities in the districts (27).

The geographical allocation was derived from the district of residence of the insured. The degree of variation was assessed using systematic component of variation (SCV) and the coefficient of variation (COV) (28). The association between the rate of coronary angiography in the 401 administrative districts and the regional demographic risk structure, the diagnosed coronary heart disease prevalence, the social deprivation and the availability of cardiac catheterization facilities was investigated in spatial-autoregressive error models (29) and spatial cross-regressive model with autoregressive errors (1).

2.3.1.2 Guideline-recommended drug therapy before percutaneous coronary intervention (Paper 2)

A second topic of interest in the context of catheterization, specifically percutaneous coronary intervention, is the treatment course before the revascularization procedure. Next to measures aimed at lifestyle-modification, drug therapy is recommended as the initial treatment approach in the management of patients with stable coronary heart disease, with revascularization procedures are reserved for patients with persistent symptoms despite optimal medical therapy (13-15, 30-32). The active ingredients of the drugs were determined using the ATC classification and the classes of substances were grouped as preferred or alternative options and as aimed of improving the prognosis of the patient (optimal medical therapy) or targeted at relieving the patient's symptoms (symptom-oriented therapy), in accordance with the guideline recommendations (2). Patients were classified as users of optimal medical therapy if, within twelve month before percutaneous coronary intervention, they had received at least one prescription of a drug aimed at lowering lipid levels and at least one prescription to relieve symptoms (2). Because relieving patients of chest pain plays a vital role in the management of stable angina pectoris, in particular in cases where revascularization is considered as a subsequent treatment, the prescription of medication to alleviate symptoms was assessed alone in an additional analysis. In this analysis of symptom-oriented therapy, special attention was paid to whether the conservative treatment options with drug therapy had been exhausted prior to percutaneous coronary intervention. Patients were considered users if, they had obtained prescriptions for at least two different drug classes of symptom-oriented therapy within twelve months prior to the procedure (2). The study population in Paper 2 (2) included patients who had received percutaneous coronary intervention in 2016 in hospital (inpatient or outpatient) or in an office-based practice. The main analysis included patients treated for stable angina pectoris, chronic ischaemic heart disease or chest pain at the time of the procedure and who had obtained a diagnosis of coronary heart disease during the observation period from 2014 to the billing quarter prior to the procedure in 2016 (2). Patients without a confirmed diagnosis of coronary heart disease and patients treated for unstable angina pectoris were examined in sensitivity analyses (2). The geographical assignment to the 401 districts was based on the place of residence of the insured. The GKV routine data set was supplemented with regional data on the density of general practitioners and specialists in internal medicine and the average number of cases treated by these physician groups (33, 34). The influence of individual demographic and clinical characteristics on prescription prevalence was assessed in a logistic regression model. Lastly, within a multi-level model, variation at the level of the administrative districts in Germany was assessed and the influence of features of local health care supply was examined (2).

2.4 Summary of results and scientific contribution

2.4.1 Paper 1

Overall, a wide variation was found in the regional rates of coronary angiography. The results of the study supported the hypothesis that the regional variation and the association of supply and need with the rate differ depending on the indication for the procedure. In the acute situation, the benefits of coronary angiography are firmly established; therefore, the variation in the rates observed among the 401 districts is comparatively low in this group. In cases with myocardial infarction the rate varies by 3.53-fold and the measured variation in the rate of coronary angiography cases with myocardial infarction is small with a COV blow 20 and SCV equal to 3.37 (1). In contrast, the rate of cases without myocardial infarction varies by 7.78-fold and the observed variation shows a SCV greater than 8 and a COV greater than 28, indicating high variation (1). The results are affirmed in the sensitivity analysis focusing on acute coronary syndrome, with the exhibited variation between the two subgroups appearing to be less pronounced. The highest variation was observed in the cases treated for stable coronary heart disease or chest pain (1). Spatial analysis by subgroup suggests a positive association between regional availability of cardiac catheterization facilities and the coronary angiography rates of non-acute cases after adjusting for the observed morbidity, whereas no such association was seen in the acute situation (1). The addition of one hospital with a catheterization facility (per 10,000) is estimated to correspond to approximately 40 additional coronary angiography cases without myocardial infarction (per 10,000 population), amounting to an 43–50% increase in the rate (1). The estimate of diagnosed coronary heart disease prevalence shows a pronounced positive association with the overall rate and all subgroups considered in the analysis. The deprivation index showed no discernible association with the overall coronary angiography rate or the rate of cases without myocardial infarction. On the contrary, it shows a significant positive association with the coronary angiography rate in cases with myocardial infarction (1). The sensitivity analysis showed similar results.

2.4.2 Paper 2

The analysis (2) showed that in patients with stable coronary heart disease drug therapy options before percutaneous coronary intervention are not entirely exhausted and that there are considerable differences in the prescription of drug therapy recommended by the guidelines in routine practice in Germany. The criterion of optimal medical therapy was met in 69% of patients in the year before the procedure. A quarter of the patients received only one of the recommended therapies considered. 6% of the patients in the sample obtained no prescription of optimal medical therapy (2). Patients with a history of myocardial infarction, previous revascularization, a disorder of the lipid metabolism, heart failure, diabetes mellitus, hypertension, or peripheral artery disease had higher odds of obtaining the optimal medical therapy (2). Above average age and a depression or dementia diagnosis were associated with odds of obtaining an optimal medical therapy prescription (2). Enrolment in a disease management programme (DMP) for coronary heart disease and more frequent visits to the general practitioner or primary care internist were associated with higher odds of being prescribed optimal medical therapy (2). At the regional level, the variables included in the model indicated no discernible influence (2).

87% of patients obtained at least one symptom-oriented therapy, and of these 44% received at least two symptom-oriented medications (2). Female gender, above average age, prior myocardial infarction and diagnosed comorbidities were associated with increased odds of obtaining a prescription for symptom-oriented therapy within the year preceding the percutaneous coronary intervention (2). Patients enrolled in a DMP, those who made frequent contacts to the general practitioner or primary care internist and those, who had additional visits to a cardiologist had higher odds of receiving symptom-oriented therapy in comparison to patients who used fewer health care services (2). The variables for regional health care supply considered in the analysis showed no associations. Nevertheless, patients in eastern German districts had higher odds of receiving a prescription for symptom-oriented therapy after controlling for individual characteristics (2).

2.5 Strength and limitations

One of the great strengths of the analyses presented in the project is the foundation on a comprehensive nationwide data set from statutory health insurers, who cover a population of approximately 42.5 million insured individuals. Owing to its special characteristics, working with GKV routine data offers both opportunities and challenges. The data can map the health care use of insured people across sectors and over time. Because of their breadth, the data allow regional analysis, which provides a nationwide picture of the provision of health services in Germany. In contrast to data collected primarily, distortions resulting from recall bias or non-response are not to be expected. The data comprise largely unselected populations, and the number of people at risk is known, which allows frequency and rate estimates to be made. The insured in the samples were allocated to the geographical location according to the district of residence, as opposed to the location where the procedure was performed (1, 2). The advantage of this type of allocation is that it avoided distorting the results to the detriment of large centres or cities and that it allows a linkage with the examined influencing factors measured at the place of residence.

However, there are a number of important limitations concerning the GKV routine data. The data do not hold information on symptoms, clinical data, or the results of non-invasive testing, nor do they include information on a patient's lifestyle. Linkage to such data would be a valuable addition in future investigations. Because this information is not available, the doctor's risk assessment cannot be reconstructed in detail based on the data. In the individual case, it is therefore impossible to determine whether the indication for coronary angiography and subsequent revascularization reflects actual need. Guidelines provide scope for decision-making, and therefore the application of guideline recommendations must be checked in each individual case. Nonetheless, it can be assumed that an exceptional course of disease progression occurs on a relatively small scale and not at the nationwide population perspective on which the two analyses are based. The regional utilisation of non-invasive diagnostics prior to coronary angiography was not included in the analysis in Paper 1, because some measures could not be depicted reliably in the GKV routine data (1). For this reason, it was not possible to assess to what extent deviations in adhering to the guidelines with regard to non-invasive diagnostics are associated with the regional variation in coronary angiography rates (1). Lastly, services that are not relevant to billing are not coded in the GKV routine data. For example, in some cases, cardiac magnetic resonance imaging (MRI) or cardiac computed tomography (CT) may be carried out instead of coronary angiography (1). In contrast to coronary angiography, cardiac MRI and CT are not regularly reimbursed in Germany. In the German health care system, self-payments are the exception. Overall user charges and out-of-pocket spending account for a comparatively low share of health expenditure (35). Based on these circumstances, we assume that the services play a negligible role and should therefore have little influence on the findings of the analysis.

The situation differs in the case of over the counter use of ASA in Paper 2, which cannot be ruled out, so it is expected that the prescription prevalence is underestimated in the analysis in Paper 2 (36). There are some other notable limitations with regard to the prescription billing data and the analysis (2). The data set does not included drugs that are administered or prescribed in hospitals (18), possibly underestimating the prescription prevalence. Since the prescription data is forwarded from the pharmacies to the health insurance companies for billing purposes, a prescription was only recorded if it was redeemed. Therefore, low prescribing can be attributed to either poor application of guideline recommendations by providers or treatment discontinuation or poor adherence of the patient (2). Some of the examined drug therapies are not disease specific, and physicians may have prescribed them aimed at patients' comorbidities, leading to an overestimation of the prescriptions that can be attributed to the diagnosis of coronary heart disease (2). In addition, the analysis does not take any intolerances or contraindications into account. Although guideline recommend alternatives are considered in the analysis, it cannot be ruled out that in certain situations both were contraindicated. The multi-level model is not taking the supply of health services in neighbouring districts into account. Hence the analysis only permits the appraisal of the impact of care in a residential district of the patient (2). Another limitation that applies to both analyses (1, 2) is the possible influence of the physicians´ coding behaviour on the documentation of the diagnoses in the GKV routine data. Regional or subject-specific heterogeneity in the documentation, may cause a misclassification of patients based on the diagnosis in the subgroups considered or in the study sample.

One major challenge in both analyses (1, 2) in the PhD project was the selection of covariates. In Paper 2 (2), the focus was not on a predefined variable. Instead, the analyses examined the association of individual and regional factors that may have an influence on the prescription of optimal medical therapy and symptom-oriented therapy. Therefore, the selection relied on the existing literature to identify potentially relevant predictors of guideline-recommended drug therapy. The selection is described in detail in the supplement to the publication. In Paper 1 (1), the aim was to investigate the effect of a specific predefined variable, namely the regional supply of catheterization facilities. Because such data are not readily available, the information was obtained from the quality reports of the hospitals (27). It has to be noted, that no information regarding office-based facilities, apart from the ones documented as working in collaboration with a hospital are listed in the reports.

The findings in Paper 1 (1) suggest a notable association between the supply of catheterization facilities in hospitals and the coronary angiography rates. Despite this, the finding does not offer evidence for supply-induced demand. This is due to the fact that, the direction of causality cannot be established using regional data. The supply cannot only influence the use of coronary angiography, but more coronary heart disease patients in one region may attract service providers, as there is a greater need. If supply assumed to be endogenous, then the estimates of the impact supply on the coronary angiography rates will be biased by any residual differences in morbidity remaining after the adjustment. The problem statement was reproduced using directed acyclic graphs (DAGs) (37), and the possibility of an estimation by means of an instrumental variable was examined. However, unlike in the case of studies of supply of ambulatory services where this problem has been addressed by instrumental variables (38, 39), we found no instrument to resolve the issue. Therefore, the analysis can only provide informed correlations. A possible objection to the presumption of endogeneity is that, there is no apparent association between the estimated diagnosed coronary heart disease prevalence and the regional supply. Furthermore, the rate of non-acute cases showed a positive association with supply, but no such relationship was observed with the coronary angiography rate of acute cases. If the association between supply and the rate of coronary angiography is indeed affected by the residual morbidity differences influencing the supply capacity, there is no explanation why this association was not observed in the acute cases. In contrast, the rate of cases with myocardial infarction indicated a positive association with the GISD, possibly reflecting the residual morbidity (1). Nonetheless, caution is advised when interpreting the relationship.

2.6 Conclusion and outlook

This project adds to the evidence base by portraying the use of selected health services in accordance with guideline recommendations for coronary heart disease and by investigating regional practice variation in Germany based on nationwide GKV routine data. First, the extent to which selected recommendations of the guidelines can be examined using GKV routine data was assessed. Second, it was assessed whether the German clinical practice mirrors selected guideline recommendations in regional analyses. Lastly, it was assessed whether there are indications that the recommendations are adhered to in varying degrees and if these differences are associated with various characteristics including the regional health care supply. In doing so, regional differences and considerable variation in health care service utilization became apparent.

Paper 1 (1) highlighted substantial regional variation in the use of coronary angiography between the 401 districts. The findings in Paper 1 (1) substantiated the assumption that situations with lesser certainty about the evidence for a particular treatment are accompanied by greater variation in its use. The results in Paper 1 (1) showed that the degree of variation and the association of the rate with supply and need differed considerably between the acute and non-acute cases. The comparison of the subgroups suggested that regional variation in the rate of coronary angiographies in the acute group are associated with need factors, while in non-acute situation, the coronary angiography rate also showed a positive association with supply. Furthermore, an association between rates of coronary angiographies and deprivation was found in acute groups, but not in the non-acute cases.

Paper 2 (2) provided a picture of guideline recommended drug therapy prior to percutaneous coronary intervention among patients with stable coronary heart disease while accounting for individual patient characteristics and the regional health care supply. The analysis showed considerable variation in the prescription of optimal medical therapy among patients with stable coronary heart disease and that the conservative therapy was not exhausted prior to revascularization. Paper 2 (2) showed that patients who received the guideline-recommended drug therapies had more comorbidities and risk factors and used a higher volume of health services. The analysis of the prescription prevalence in eastern and western German districts revealed a notably higher prevalence in the eastern districts. These differences could result from several reasons, such as different patient or provider preferences, different drug budgets, differences in the market penetration of medications or they might reflect preferences differences in the use of percutaneous coronary intervention.

Lastly, the analyses presented here shed further light on methodological challenges in the analysis of guideline-recommended care based on GKV routine data. The advantages and methodological challenges such as study design, data preparation, supplementation, analysis, and possibility to depict of recommendations in the coronary heart disease care guidelines were discussed. The possibility of regional evaluation and analysis of the care situation of different patient groups was also examined as part of the PhD project. Owing to their cross-sectoral information and the national scope, these data are very well suited for analyses of the broad reality of care. The analysis therefore not only allows an assessment of the routine health care of patients with coronary heart disease in Germany, but also allows the results to be viewed in the international context. Drug prescription data in particular are well suited for analysis purposes because they contain a lot of detailed and date-specific information. This also applies to procedures in the inpatient and outpatient hospital sector and, to a lesser extent, for those performed in outpatient medical practices. The analyses also demonstrate how GKV routine data can be supplemented with data from other sources. There is a further need for research in the methodological standardization of health services research with GKV routine data. Also, enhancing the GKV routine data through linkage with other primary and secondary data can counteract the described limitations. The linkage of GKV routine data to primarily collected data of clinical parameters, diagnostic results, outcomes, or patient preferences could add to the informative value of the analyses and would make it possible to represent the patient's perspective. Also, the application of combinations of quantitative and qualitative research methods could further enhance such analyses.

Health services research in the context of medical guidelines is increasing transparency in the health care system. Providing such information may reduce the asymmetric distribution of information among all players in the health care system. Stakeholders can use this information about the real care situation to make recommendations for action, allocation decisions and to develop targeted measures. GKV routine data represent a valuable data basis for increasing transparency and quality in the health care system, as they can depict the care process realistically, across sectors and along the patient path. The findings of this PhD project offer insight into the provision of health services and suggest that there may be opportunities to improve the care of patients with stable coronary heart disease in Germany. These results can be used to formulate hypotheses on the topic, inform international comparisons and can provide a platform for targeted regional health services research. In view of the constantly evolving field of research, the present PhD project only provides a snapshot regarding the possibilities of research considering guideline-recommended care based on GKV routine data.

3. Paper 1

Frank-Tewaag *et al.*
BMC Cardiovascular Disorders (2022) 22:72
https://doi.org/10.1186/s12872-022-02513-z

BMC Cardiovascular Disorders

RESEARCH ARTICLE **Open Access**

Regional variation in coronary angiography rates: the association with supply factors and the role of indication: a spatial analysis

Julia Frank-Tewaag[1,2,3*], Julian Bleek[4], Christian Günster[5], Udo Schneider[6], Dirk Horenkamp-Sonntag[6], Ursula Marschall[7], Sebastian Franke[1], Kathrin Schlößler[8], Norbert Donner-Banzhoff[9] and Leonie Sundmacher[1]

Abstract

Background: Coronary angiographies (CAs) are among the most common diagnostic procedures carried out in German hospitals, and substantial regional differences in their frequency of use have been documented. Given the heterogeneity with regard to the expected benefits and the varying scope for discretion depending on the indication for the procedure, we hypothesized that the observed variation and the association of need and supply factors differs by indication for CA.

Methods: We investigated the correlation between supply factors and the regional rates of CAs in Germany while controlling for need using spatial-autoregressive error models (SARE) and spatial cross-regressive models with autoregressive errors (SCRARE). The overall rates of CAs and the rates in specific patient subgroups, namely, patients with and without myocardial infarction (MI), were calculated based on a comprehensive set of nationwide routine data from three statutory health insurances at the district level.

Results: Although little variation was found in cases with MI, considerable variation was seen in the overall cases and cases without MI. The SARE models revealed a positive association between the number of hospitals with a cardiac catheterization laboratory per 10,000 population and the rates of overall cases and cases without MI, whereas no such relationship existed in cases with MI. Additionally, an association between regional deprivation and the rates of CAs was found in cases with MI, but no such association was seen in cases without MI.

Conclusions: The results supported the hypothesis that the relative association of need and supply factors differed by the indication for CA. Although the regional differences in the frequency of use of CAs can only be explained in part by the factors examined in our study, it offers insight into patient access to and the provision of CA services and can provide a platform for further local research.

Keywords: Coronary heart disease, Coronary angiography, Clinical practice variation, Indication, Regional analysis

Introduction

Coronary angiography (CA) is an invasive diagnostic procedure that aids in making the decision between conservative treatment only or a revascularization procedure, namely, percutaneous coronary intervention (PCI) or bypass surgery (CABG). Current guidelines emphasize the role of CA in preparing for treatment while limiting purely diagnostic indications [1–4]. Regional variation

*Correspondence: julia.frank-tewaag@tum.de
[1] Technische Universität München, Uptown München Campus D, Georg-Brauchle-Ring 60/62, 80992 München, Germany
Full list of author information is available at the end of the article

in the utilization of CA and PCI has been documented across different countries and health systems [5–14]. CAs and PCIs are among the most common diagnostic procedures carried out in German hospitals [15], and the rates of these procedures in Germany have been deemed to be rather high in comparison with those documented in other European health systems [16]. In addition, substantial regional differences in the frequency of use of CAs and PCIs have been documented in Germany [17, 18]. It has therefore been discussed repeatedly whether these findings truly reflect differences in medical need [16–18].

Some regions, for example, may exhibit higher rates of CAs because of greater demand in these localities. Demand, in the broadest sense, reflects the patient-related factors that influence the actual or perceived need for a procedure. These factors include the incidence of a treatable disease, the rate at which the disease is detected prior to the procedure and the willingness of patients to undergo the procedure [19]. However, it may be the case that factors other than patients' needs or preferences are driving treatment decisions, particularly when the procedure in question leaves room for discretion. Piedmont et al. [18] found an almost linear association between the regional rate of CAs in the districts of the German federal state of Saxony-Anhalt and the number of cases without therapeutic consequences. The authors noted that they were unable to satisfactorily assess the influence of regional supply structures on the frequency of use, but they pointed out that the wide range in the proportion of procedures without therapeutic consequences indicates an influence of supply-related factors. The number of catheterization facilities in Germany has increased in recent years, and needs-based large equipment planning in hospitals (§ 122 SGB V) was once envisaged but was cancelled without replacement in 1997 [20].

Wennberg et al. [21] suggested a relationship between the availability and quality of evidence to support a particular intervention and the variation in its use. When there is greater uncertainty about the evidence base for a procedure, there is more likely to be variation. The authors distinguished among three categories of care. Effective care comprises services that are supported by a well-established evidence base for their efficacy. Preference-sensitive care includes services where at least two valid alternative strategies for action are available, and the decision involves a trade-off because the risks and benefits of the options differ. Supply-sensitive care occurs primarily when there is a broad scope for decision-making due to a lack of evidence and guidelines to inform best practice or greater medical uncertainty [21, 22]. CAs and PCIs are ideal for the study of medical practice variations because they exhibit considerable heterogeneity with regard to their benefits across different patient groups, and the evidence and appropriateness criteria provide considerable opportunity for discretionary judgment depending on the indication for the procedure. For patients presenting with symptoms of acute coronary syndrome (ACS) or myocardial infarction (MI), the benefits of PCI are well established [23, 24]. In patients with chronically stable coronary heart disease (CHD), the decision is much less clear-cut [25, 26]. In these non-acute situations, the use of elective CA and PCI is preference sensitive because alternative treatment strategies exist, and the decision to undergo the procedure involves a trade-off between the risks and benefits. Owing to the broader scope for decision-making and the accompanying uncertainty in these circumstances, the available supply capacity may exert an influence on utilization.

Given the differences, we hypothesized that the observed variation and the possible association of need and supply factors differ by indication for CA. We therefore aimed to investigate regional variation in the rates of CAs and the correlation between supply factors and the regional rates of the procedure in patients with and without MI in Germany while controlling for the actual need. To this end, the overall rates of CAs and the rates in specific patient subgroups were calculated based on a unique, comprehensive set of nationwide regional routine data from statutory health insurances. Regional differences in the observed rates were scrutinized in small-area analyses at the district level with empirical Bayes (EB) smoothing to account for variance instability resulting from the differing sample sizes.

Methods

Data and study population

The analysis was based on a comprehensive set of linked nationwide billing data from three statutory health insurances for the years 2014 to 2016, which equated to a total insured population of almost 42 million. The sample cohort included patients who were aged 18 years or older and who underwent CA in 2016 in the hospital on an inpatient or outpatient basis (OPS 1–275.0 up to 1–275.5). In addition, because not only hospitals play a role in the provision of the procedure in Germany, patients who underwent CA in an office-based practice (EBM 34291) were also included in the sample. Furthermore, to be considered, patients needed to be insured for at least 360 days. Patients with a shorter insurance period were only considered for the analysis if the reduction in the duration of insurance occurred because the patients died at the time of the CA procedure or after. Insured individuals who switched their insurance between 2014 and 2016 and patients without details of their place of residence or those with implausible information were excluded from the analysis. We carried out the analysis at the billing case level. If a patient had multiple recorded procedures within a billing case, they were only counted once. Several treatment cases per patient on the same day of treatment were also considered as one case.

Patient subgroups by indication

The patient subgroups by indication for CA were determined by means of the main inpatient diagnosis, an outpatient hospital diagnosis or a secured office-based diagnosis in the treatment case of the CA. In the main analysis, we present the overall rates of CAs, the rates of cases with MI (ICD-10: I21.* or I22.*) and the rates of cases without MI. This allowed for comparison of the rates in a situation of effective care (MI) in which a strong evidence base for efficacy guides the treatment decisions, as opposed to situations where greater uncertainty is present (cases without MI). To assess the plausibility of the results, in a sensitivity analysis, we extended the definition of an acute indication to ACS (ICD-10: I21.*, I22.*, I20.0 or I20.1). Again, the rates of cases without ACS and the rates of cases with ACS were examined. Last, cases who were treated for stable CHD or chest pain (CP) (ICD-10: I20.8, I20.9, I25.0, I25.1, I25.5, I25.8, I25.9 or R07.*) were included in the sensitivity analysis.

Geographical assignment

The insured patients in the study sample were assigned to a geographical location based on their district of residence, not the treatment locations. In Germany, a district is an administrative unit between federal states and the local municipal levels. The advantage of this allocation was that a distortion of the results to the detriment of the independent cities was prevented, and the factors considered in our analysis were measured at the place of residence. The spatial allocation was based on the official district key (area status on 31st of December 2016), taking into account the territorial reform in Lower Saxony on 1st of November 2016. We used the information available at the time of the first procedure in 2016; if the information was missing, the last available information on the patient's place of residence was considered.

Rates, standardization and assessment of variation

The rates were calculated using the total insured populations of the three statutory health insurances as the denominator. To address the variance instability resulting from the differences in population size, we applied EB smoothing [27]. We calculated the rates per 10,000 population standardized for differences in age and sex by means of the direct and indirect method based on the reference population for Germany as of the reporting date 31.12.2015. We measured the relative degree of variation using the coefficient of variation (COV) and the systematic component of variation (SCV) [28]. In general, SCV values above 5 are indicative of high variation, whereas SCV values above 10 point toward very high variation [19].

Empirical model

Dependent variable

We use the crude unadjusted CA rate as the dependent variable in the empirical model because the use of standardized rates as the outcome may lead to biased estimates when the relationship between the standardization parameters, in this case age and sex, and other explanatory variables is not taken into account [29, 30].

Independent variables

To incorporate the demographic risk structure of the regional population in each district, we included the proportion of residents in each age-sex group in our model. Because there were 12 age-sex groups, 11 independent variables were used in the regression model, and the age-sex group 'females under the age of 40 years' constituted the reference group. The actual occurrence of treatable disease and the rate at which it was detected was unknown, but it could be approximated in the routine data through the diagnosed prevalence of CHD in the districts. We estimated the diagnosed CHD prevalence in the routine data as the proportion of individuals in the total sample of insured with a confirmed diagnosis of CHD (ICD-10: I20–I25, an inpatient primary or a secondary diagnosis or a confirmed office-based diagnosis in at least two quarters) during 2016. In addition, diagnosed risk factors, namely, type II diabetes and hypertension, were considered as variables. However, the variables showed a high correlation with the estimated diagnosed CHD prevalence; they were not included in the model to avoid problems associated with multicollinearity. Other risk factors related to lifestyle, such as smoking, cannot be derived from routine data. However, it has been shown that these risk factors are highly correlated with deprivation at the district level. For this reason, the German Index of Social Deprivation (GISD) 2012, which has been validated in patient groups with CHD, was incorporated as an additional factor to mediate the residual morbidity risks that remained after accounting for the disease prevalence [31]. In addition, it must be noted that the perceived need and preference of the patients could not be estimated. However, these factors were modeled as unobserved heterogeneity. To assess the impact of regional health care supply, we included information on the availability of hospitals with cardiac catheterization laboratory facilities per 10,000 population in the model. This information was extracted from the hospitals' quality reports [32]. The data did not contain information on office-based facilities apart from those listed in the reports as working in collaboration with a hospital. Additionally, the number of catheterization laboratories within a given facility was unknown.

Spatial model

The estimation model was formulated as a generalized, spatial, two-stage, least square model with spatial-autoregressive disturbances [33] based on the spatial models of Cliff and Ord (1973) [34]. We assumed that a spatial error model, as opposed to a spatial lag model, was suitable to describe the process underlying our data because we believe that it is unlikely that the error term is distributed independently across the districts. The spatial error model was consistent with the assumption that spatial correlation arises from the geographical concentration of unobservable factors, such as unmeasured health status, risk factors or patient preference, or in a situation where exogenous shocks in one district impinge on neighboring districts [35, 36]. We did not assume that the CA rate in one district was directly affected by the rate in another district and therefore discarded the spatial lag model. Regional spillover effects might be present if the use of health services was measured in the district of the service provision. However, because we measured the rates at the patients' places of residence and not the providers' locations, such spillover should not be of relevance. Our estimation Model A was therefore simplified to a spatial-autoregressive error (SARE) model, in which only the error terms were spatially correlated [37]. The definition of the individual districts as the catchment area for the supply of medical services might be regarded as too small to accurately reflect the supply of CAs. Therefore, our estimation Model B was formulated as a spatial cross-regressive model with autoregressive errors (SCRARE) [38], which included a spatial lag of the independent variable measuring the availability of hospitals with cardiac catheterization laboratory facilities. This approach took into account that the supply in neighboring districts also affects the rates of CAs. To verify the theoretical consideration and presence of spatial autocorrelation and to select the appropriate model for estimation, we estimated ordinary least square (OLS) regression models and performed the Lagrange Multiplier test [39]. In both models, the weight matrix that reflected the relationship between spatial units was a queen contiguity matrix, which defined neighbors as sharing a common edge or a common vertex [27]. To allow for a straightforward interpretation of the model parameters, the spatial weighting matrix was normalized. Different normalization methods make different assumptions about the spatial interdependence of observations. A row-standardized spatial weights matrix implies that every region is subject to the same total amount of influence from all other regions [40]. Unless this implicit assumption is clearly suggested by economic theory, row normalization should not be applied [41, 42]. Felder and Tauchmann [43] that it is debatable whether the assumption that spatial interdependence is of equal relevance to all regions holds in the case of the German administrative districts because the districts, as spatial units, vary with respect to their interlinkage with the rest of the country and in terms of their remoteness. They proposed eigenvalue normalization [42], which allows for spatial dependence to be differently important across observations. In the present analysis, we applied both row- (*Wr*) and eigenvalue-normalization (*We*) and contrasted the results obtained under the diverging assumptions. The analyses were performed in Stata SE16 and GeoDa.

Results

Study sample

The dataset comprised nationwide linked billing data from the statutory health insurers AOK, BARMER and Techniker Krankenkasse from approximately 42.5 million individuals. In 2016, a total of 379,625 patients in the sample dataset underwent CA at least once. Of these patients, 269 (0.07%) were excluded because of incomplete or implausible information. For 584 patients (0.15%), information on the patients' districts of residence was missing at the time of the first procedure in 2016; the last available information was considered for the geographic assignment.

Frequency, characteristics and regional CA rates

In total, in 2016, 379,356 patients in our analysis sample had undergone CA at least once. Expressed as the number of cases (hospital or office-based practice visits with at least one CA procedure), this amounted to 425,163 procedures among 41,739,344 (1.02%) insured patients. Extrapolated to the total German population, this resulted in an absolute number of 753,135 patients who underwent CA at least once and 844,771 CA cases. Table 1 shows the frequencies of CA and revascularization procedures (PCI or CABG) by health care sector and the subgroups by treatment diagnoses in the main analysis. The majority of CAs were carried out in a hospital setting and in cases without MI. An intervention was performed in more than 40% of cases. Some 75,542 (17.77%) cases were treated for MI, of which over 99% were treated in an inpatient hospital setting (see Additional file 1: Table A2 for the sensitivity analysis).

Table 2 summarizes the crude and adjusted CA rates and the measures of variation for the cases overall and the cases without MI and with MI. At the district level, the direct standardized rate (DSR) for the overall cases

Table 1 Frequency and characteristics of cardiac catheterization by treatment setting

		Hospital		Office-based practice
		Inpatient hospital	Outpatient hospital	
Cases	n (column %)	N (row %)		
CA	425,163	369,882 (87.00%)	19,317 (4.54%)	35,964 (8.46%)
PCI*	168,418 (39.61%)	163,503 (97.08%)	118 (0.07%)	4797 (2.85%)
CABG*	4642 (1.09%)	4642 (100.00%)	0 (0.00%)	0 (0.00%)
*Treatment diagnosis***				
Cases with MI	75,542 (17.77%)	74,983 (99.26%)	62 (0.08%)	497 (0.66%)
Cases without MI	349,621 (82.23%)	294,899 (84.35%)	19,255 (5.51%)	35,467 (10.14%)

CA, coronary angiography; CABG, coronary artery bypass graft; MI, myocardial infarction; PCI, percutaneous coronary intervention

*In the same treatment case

**Inpatient main hospital diagnosis, outpatient hospital diagnosis, confirmed ambulatory diagnosis in treatment case

Table 2 Crude rate, direct standardized rate (DSR) and measures of variation

	Cases	Cases without MI	Cases with MI
Crude data			
Number of CAs	425,163	349,621	75,542
Crude rate per 10,000 population	101.86	83.76	18.10
Age-sex DSR in 401 districts per 10,000 population			
Median	101.67	82.82	17.41
Mean (SD)	102.69 (25.98)	84.32 (24.18)	17.61 (3.44)
Min	46.79	27.08	9.58
Max	229.19	210.62	33.77
Measures of variation			
COV	25.29	28.68	19.53
SCV	6.44	8.26	3.37

CA, coronary angiography; COV, coefficient of variation; DSR, direct standardized rate; MI, myocardial infarction; SCV, systematic component of variation; SD, standard deviation

ranged from 46.79 to 229.19, with a mean of 102.69 cases per 10,000 population. The observed variation in the overall rate of CA cases showed a COV of over 25% and a SCV over 6, which suggests high variation. When looking at the subgroups by treatment diagnosis, the difference in the extent of variation at the level of the 401 districts became apparent. The rate of cases with MI varied 3.53-fold, and the rate of those without MI varied 7.78-fold. The variation measured in the rate of CA cases with MI was relatively low (COV = 19.5 and SCV = 3.37) in comparison with that of the cases without MI (COV = 28.68 and SCV = 8.26). The findings for MI were confirmed by the sensitivity analysis considering cases with and without ACS, with the observed difference in variation between the two groups being less pronounced, and the measures of variation showed the highest values in cases with stable CHD or CP (see Additional file 1: Table A3).

Figure 1 depicts the distribution of the CA rates of cases overall and cases with and without MI expressed as the ratio of rates (RR) to the respective national average across the districts of Germany. The distribution of high rates in overall cases showed a similar pattern compared with cases without MI, whereas cases with MI showed a different pattern. The maps also showed the wider distribution of the overall cases and the cases without MI in comparison with cases with MI. This is also illustrated in Fig. 2, which depicts the DSR for the three groups in the 401 districts per 10,000 population (see Additional file 1: Figure A1 for the DSR maps).

Model results

The Lagrange Multiplier test verified the theoretical consideration regarding the model specification. Table 3 shows the regression results of Model A (SARE) and Model B (SCRARE) with the two specifications of the weight matrix, *Wr* and *We*. ρ, the estimated value of the spatial autocorrelation parameter, was positive and significant in all models, indicating moderate spatial autoregressive dependence in the error term. In other words, an exogenous shock to one district would cause moderate changes in the CA rate in the neighboring districts. The differences between both models and the matrix specifications were rather small. The specification of the weight matrix by means of eigenvalue-normalization (*We*) showed a higher Peusdo-R^2 value compared with the row-normalization (*Wr*), signaling a slightly superior model fit. Estimation Model B, which included a spatial lag of the independent variable measuring the availability of hospitals with cardiac catheterization laboratory facilities, yielded similar direct effects in all patient subgroups.

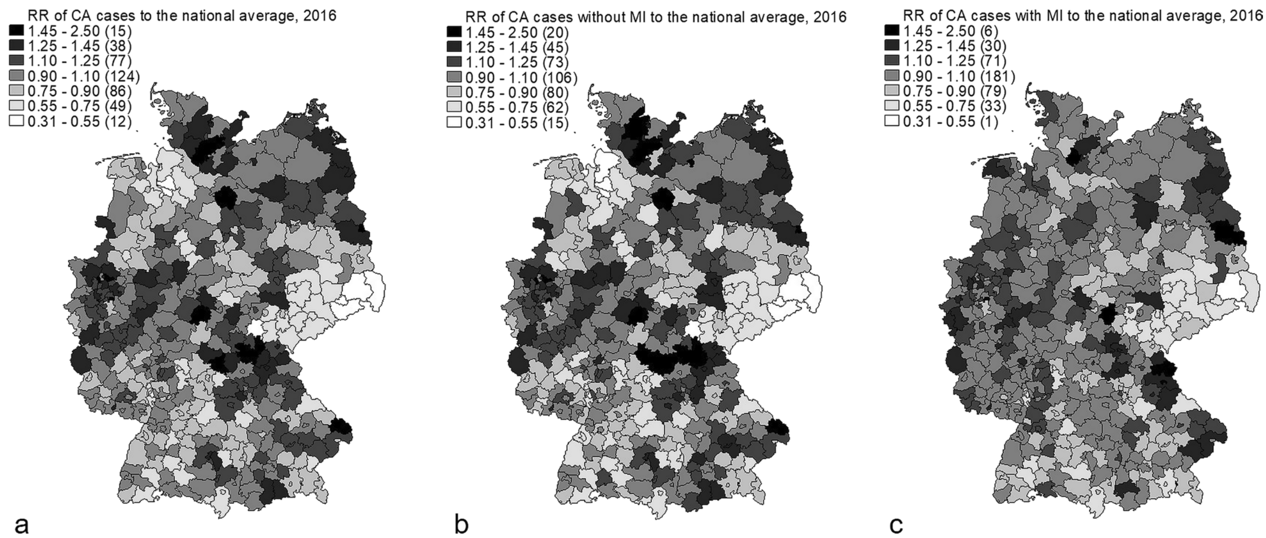

Fig. 1 Map of CA **a** cases overall, **b** cases without MI and **c** cases with MI. Ratio of rates (RR) for the respective national average, 2016, classification method: custom; number in brackets displays the number of districts belonging to each class. *Source*: own depiction

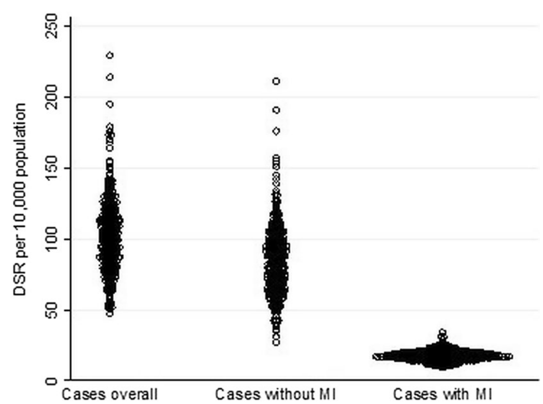

Fig. 2 Direct standardized CA rate per 10,000 population by treatment diagnosis, 2016. Each dot represents one of the 401 districts

The coefficients of the cross-regressive effect of the availability of hospitals with a cardiac catheterization laboratory (W × Cath labs) were all nonsignificant, except for the CA rate of cases without ACS and cases with CHD and CP (see Additional file 1: Table A4). In terms of the explanatory power of the examined factors regarding the regional variations in the patient subgroups, both models and the weight matrix specifications arrived at similar conclusions. We therefore focused primarily on reporting the results of Model A because Model B, which included the spatial lag of the independent variable measuring the availability of hospitals with cardiac catheterization laboratory facilities, did not add substantial further information.

With regard to Model A, the estimate of the prevalence of diagnosed CHD showed a strong positive association with the rates of CAs in the overall rate and all the patient subgroups and appeared to be a good measure for adjusting for the morbidity differences among the districts. An increase of 1% in the proportion of the population with a confirmed diagnosis of CHD in a district led to an estimated 10.01 additional CAs per 10,000 population (increase of approximately 10%) in the overall rate. The model showed a strong positive correlation between the number of hospitals with a cardiac catheterization laboratory per 10,000 population and the overall rate of CAs. One additional hospital with catheterization facilities per 10,000 was estimated to equate to 41–46 additional cases per 10,000 population, which corresponds to a 38–43% increase in overall cases. In contrast, no association was found in cases treated for MI, whereas cases without MI showed a strong positive correlation between the number of hospitals with a cardiac catheterization laboratory per 10,000 population and the rate of CAs. One additional hospital with catheterization facilities per 10,000 was estimated to equate to 38–43 additional cases without MI per 10,000 population, which amounts to a 43–50% increase in the rate. Our sensitivity analysis with ACS and stable CHD or CP cases showed similar results (correlation in cases without ACS and in cases with CHD or CP; no correlation in cases with ACS; see Additional file 1: Table A4). The GISD exhibited no significant association with the overall CA rate or cases without MI. In contrast, it showed a positive significant correlation with the CA rate in cases treated for MI (and ACS, see Additional file 1: Table A4).

Table 3 Model results

	Cases overall				Cases without MI				Cases with MI			
	Model A (SARE)		Model B (SCRARE)		Model A (SARE)		Model B (SCRARE)		Model A (SARE)		Model B (SCRARE)	
	Wr	*We*	*Wr*	*We*	*Wr*	*We*	*Wr*	*We*	*Wr*	*We*	*Wr*	*We*
Observations	401	401	401	401	401	401	401	401	401	401	401	401
Pseudo R-squared	0.4186	0.4265	0.4261	0.4352	0.3813	0.3894	0.3895	0.3992	0.3986	0.4005	0.3995	0.4023
β (SE)												
Estimate of CHD prevalence[a]	10.01 (0.88)***	10.48 (1.63)***	9.87 (0.88)***	10.38 (0.88)***	8.99 (0.81)***	9.44 (0.81)***	8.87 (0.81)***	9.35 (0.81)***	1 (0.14)***	1.01 (0.14)***	0.99 (0.14)***	1 (0.14)***
GISD 2012	0.16 (0.1)	0.1 (0.11)	0.15 (0.1)	0.11 (0.1)	0.13 (0.09)	0.07 (0.09)	0.12 (0.09)	0.08 (0.09)	0.04 (0.02)**	0.04 (0.02)**	0.04 (0.02)**	0.04 (0.02)***
Cath labs[b]	40.62 (16.33)**	45.92 (19.83)**	53.41 (18.16)***	56.68 (18.32)***	37.64 (14.96)**	43.36 (15.77)***	49.34 (16.79)***	53.53 (16.95)***	2.91 (2.87)	2.97 (2.91)	3.35 (2.92)	3.49 (2.95)
W × Cath labs[b]			77.18 (47.71)	80.41 (49.84)			68.44 (44.18)	74.64 (46.56)			6.35 (7.3)	7.59 (7.14)
Constant	−143.81 (165.58)	−174.98 (142.44)	−167.02 (165.36)	−170.68 (173.94)	−103.5 (151.88)	−147.53 (160.93)	−123.82 (151.71)	−143.93 (160.46)	−20.05 (28.46)	−15.35 (28.81)	−21.27 (28.46)	−14.21 (28.78)
ρ	0.67 (0.05)***	0.72 (0.06)***	0.66 (0.05)***	0.71 (0.06)***	0.68 (0.05)***	0.72 (0.06)***	0.68 (0.05)***	0.72 (0.06)***	0.3 (0.06)***	0.31 (0.09)***	0.3 (0.06)***	0.31 (0.09)***

Coefficients for age and sex groups not reported (see Additional file 1: Table A1)

β, regression coefficient; GISD, German Index of Social Deprivation; MI, myocardial infarction; ρ, spatial autocorrelation parameter; SE, standard error

***$p<0.01$, **$p<0.05$, *$p<0.1$

[a] Proportion of individuals in the total sample of insured with a confirmed diagnosis of CHD in 2016

[b] Per 10,000 population

In Model B, the coefficients of the cross-regressive effect of the availability of hospitals with a cardiac catheterization laboratory (W × Cath labs) show no significant association in the groups in the main analysis. However, the sensitivity analysis of cases without ACS in Model B showed a positive association between both the availability of hospitals with cardiac catheterization laboratory facilities in the districts and the spatially lagged variable for both weight matrix specifications. This finding suggests that, next to the local influence of supply, the available capacity in neighboring districts also affected the rates of CAs in this subgroup. In cases with stable CHD and CP, Model B with the eigenvalue-normalization weight matrix (*We*) indicated a positive association, whereas no significant association was found in the model with the row-normalized weight matrix (*Wr*) specification (see Additional file 1: Table A3).

Discussion

Examining the rates of CAs in Germany based on a comprehensive set of nationwide routine data from statutory health insurances, we found substantial regional differences in utilization among the 401 districts. As we hypothesized, the observed variation differed among the subgroups based on the indication for treatment. In the case of MI (and ACS), the indication for CAs is unequivocal, and the benefits of intervention are well established. There is, consequently, comparably little variation in the observed rates of the procedure among the districts in these groups. In contrast, much higher variation was found in the cases without MI or ACS, and the highest variation was found in the rate of cases with stable CHD or CP.

In the spatial regression model that allowed for the spatial correlation of the error terms, we investigated the association of this variation in the rate among the districts and supply factors while controlling for need in a given locality. CHD morbidity showed a strong association with the regional rates of CAs in all the investigated subgroups. In addition, an association between regional deprivation and the rates of CAs was found in the acute cases, but no such association was seen in the other groups. By using a nationwide dataset and adding information extracted from the quality reports of the hospitals on the availability of hospitals with cardiac catheterization laboratory facilities per 10,000 population in the model, we were able to investigate the association between the regional health care supply and regional CA rates. Our findings suggest that after adjusting for the observable morbidity of the population, there was a positive correlation between the overall regional rates of CAs and the availability of hospitals with catheterization facilities. The analysis by subgroups based on the treatment diagnosis revealed a positive association between regional capacity and the rates of nonacute cases, whereas no such relationship was seen in the cases treated for MI (or ACS). The results supported the hypothesis that the association of need and supply factors differed by indication for CA, reflecting the differences with regard to the expected benefits and the uncertainty surrounding the treatment decision. In addition, the findings from the SCRARE model suggested that an indirect effect through the supply of neighboring districts might be at play in the subgroups of cases excluding ACS and possibly those with stable CHD or CP.

Piedmont et al. [18] studied the rate of utilization and the therapeutic consequences of CAs in the districts of the federal state of Saxony-Anhalt, Germany, and found that the considerable variation could not be explained by demographic differences. They also found that an almost linear association was seen between the regional frequency of CAs and the number of cases without therapeutic consequences within 12 months. The authors noted that they were unable to satisfactorily assess the influence of regional supply structures on the frequency of use because of a lack of data, but they pointed out that the wide range in the proportion of procedures without therapeutic consequences points toward an influence of supply-related factors. The relationship between the use of CA and regional capacity has been studied in the US [14]. The authors compared the association of per capita catheterization laboratories, per capita cardiologists and multi-provider markets with the utilization rates for CA in northern New England, USA. They found that variation in the use of the invasive cardiac procedure was strongly associated with the population-based availability of catheterization facilities and multi-provider markets and was unrelated to the supply of cardiologists or need. Our analysis revealed a similar relationship for the overall rate in Germany. In addition, we found that the relative association of the supply and need factors varied depending on the patient subgroup.

There may be reasons beyond population morbidity and supply that explain why the utilization of CA is higher in some districts than in others. For example, because the demand for the procedure is influenced by not only the actual need but also the perceived need, one explanation for the existing variations could be differences in patient preference. Patients sometimes appear to hold a more optimistic view of the marginal benefits of the treatment. For example, the COURAGE trials showed that for patients with stable angina, PCI provided no benefit in terms of survival or major cardiovascular events, although it did reduce pain and improve functioning [44]. In a matched survey of patients and physicians in one teaching hospital published by Rothberg et al. [45], physicians understood this evidence from the COURAGE trial; however, their patients falsely interpreted the results as a protective effect with regard to mortality and the risk of MI. Similarly, Kureshi et al. [46] concluded that patients had a poor understanding of the benefits of elective PCI, with significant variation across sites after conducting interviews with 991 patients with stable CHD undergoing elective PCI in 10 US academic and community hospitals. They therefore recommended that the anticipated benefits should be explained and discussed in detail before performing PCI. However, it is unlikely that the large variation observed across regions can largely be explained by individual patient preferences; instead, the variation is likely to be a combination of patient and physician preferences for a procedure. This is not 'supplier-induced demand' per se, but presumably, a patient forms beliefs of the expected marginal health benefit in part based on the expertise of their treating physician. Kureshi et al. [46] noted that wide variability existed in the ways in which hospitals obtained informed consent, and their findings suggested that hospital-level interventions in the structure and processes of obtaining informed consent for PCI might improve patient comprehension and understanding. Herwig and Weltermann [47] aimed to investigate patient-driven factors promoting suspected overuse in exploratory qualitative interviews with 25 patients suffering from CHD who had undergone at least one cardiac catheterization in two German teaching practices. The authors identified six patient factors that contributed to or prevented the use of catheterization: namely, the unquestioned acceptance of prescheduled appointments for procedures/convenience; disinterest in and/or lack of disease-specific knowledge; helplessness in situations with varying opinions on the required care; fear of cardiac events; the patient–physician relationship; and a patient's experience that repeat interventions did not result in a change in health status or care. They concluded that most patients trusted their treating physicians' recommendations for repeat CAs even if they were asymptomatic and that strategies to align physician adherence with guidelines and corresponding information to improve patient comprehension and understanding are needed.

Limitations

Our findings suggest a strong association between CA rates and the supply of hospitals with catheterization facilities. However, this result does not provide causal evidence for supply-induced demand because we cannot establish the direction of causality based on regional data. Therefore, our regional analysis can only establish informed correlations. One reason for this could be that not only does supply influence the utilization of CA but also, conversely, more CHD patients in an area may attract more specialized physicians and facilities that can provide treatment in the region. If we presume supply to be endogenous, then any residual differences in regional health status that remain after adjustment for the observable factors will bias estimates of the impact of the availability of cardiac catheterization laboratories on CA rates. One objection to the presumption of endogeneity due to CHD patients attracting more specialized physicians is that there is no apparent association between the distribution of the regional supply and the estimate of the prevalence of diagnosed CHD. In addition, the overall rate and the rate of cases without MI (and without ACS and cases with stable CHD or CP) showed a positive association with the availability of hospitals with catheterization facilities; no such relationship was seen in the rate of cases with MI (and ACS). If the observed relationship between the rate of utilization and supply is indeed driven by the residual unobserved differences in CHD morbidity exerting an influence on regional capacity, there is no explanation as to why this association would not become apparent in the subgroups with MI (and with ACS). In contrast, the rate of cases with MI (and with ACS) showed a positive correlation with regional deprivation, possibly capturing the residual morbidity risks related to lifestyle. Nonetheless, caution is advised with regard to the interpretation of the relationship.

There are some other important limitations of the study. Although the available data on hospitals with catheterization facilities allow an assessment of the association with supply, the data did not contain information on office-based facilities, except for those listed in the reports as working in collaboration with a hospital. In addition, the number of catheterization laboratories within a given facility, details on the equipment and occupancy and the travel distance to the facilities were unknown. Such information could enhance the analysis and possibly contribute to a better understanding of the variation in the rates in the districts.

Additionally, the routine data from the statutory health insurances did not contain clinical data or information on symptoms and the results of noninvasive testing prior to the procedure. Such information would be a valuable addition for further investigation. Additionally, regional differences in the coding practice of diagnoses may exist, which could exert an influence on the classification of the patient groups. In some cases, cardiac computed tomography (CT) or cardiac magnetic resonance imaging (MRI) may be performed instead of invasive CA. However, unlike CA, cardiac CT and MRI are not yet part of the reimbursement catalog of services of the statutory health insurances in Germany and are not regularly reimbursed. Therefore, we assumed that these factors play a negligible role in the care of statutory health insurance patients and should have a very limited influence on the results of the study. Last, the local supply and use of noninvasive diagnostics before CA was not included as an observed variable in this analysis because some of these services could not be reliably mapped in the routine data. Therefore, we were unable to assess whether, and to what extent, structural deficits or problems with guideline adherence with respect to noninvasive diagnosis are associated with the observed regional variation.

Conclusion

Our study highlighted large regional differences in the overall utilization of CA and different degrees of variation depending on the indication for the procedure. In addition, it demonstrated correlations between the overall rate and the regional health care supply while controlling for need in a given locality. Our findings for cases with and without MI suggested that, although regional differences in the rate of CAs in an acute situation are driven by need factors; in nonacute cases, supply factors also showed an association with utilization. Additionally, an association between regional deprivation and the rates of CAs was found in acute cases, but no such association was seen in the nonacute groups. Although our study can only establish informed correlations, it offers insight into patient access to and the provision of CA services, and can provide a platform for further local research to explain the mechanisms guiding regional variation in the use of CA in Germany.

Abbreviations

CA: Coronary angiography; SARE: Spatial-autoregressive error models; SCRARE: Spatial cross-regressive models with autoregressive errors; MI: Myocardial infarction; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass grafting; SGB: Sozialgesetzbuch (Social Security Code); ACS: Acute coronary syndrome; CHD: Coronary heart disease; EB: Empirical Bayes; OPS: Operationen- und Prozedurenschlüssel (Operation and Procedure Code); EBM: Einheitlicher Bewertungsmaßstab (Uniform Value Scale); CP: Chest pain; COV: Coefficient of variation; SCV: Systematic component of variation; ICD-10: International Statistical Classification of Diseases and Related Health Problems, 10th version; GISD: German Index of Social Deprivation; OLS: Ordinary least square; DSR: Direct standardized rate; RR: Ratio of rates.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12872-022-02513-z.

Additional file 1. Additional data and sensitivity analysis.

Acknowledgements

Not applicable.

Authors' contributions

JFT: Conceptualization, Methodology, Data curation, Formal analysis, Validation, Visualization, Writing- Original draft preparation; JB: Conceptualization, Data curation, Writing—review & editing; CG: Conceptualization, Writing—review & editing; US: Conceptualization, Data curation, Writing—review & editing; DHS: Conceptualization, Data curation, Writing—review & editing; UM: Conceptualization, Data curation, Writing—review & editing; SF: Data curation, Writing—review & editing; KS: Conceptualization, Project administration, Writing—review & editing; NDB: Conceptualization, Funding acquisition, Writing—review & editing; and LS: Conceptualization, Funding acquisition, Methodology, Supervision, Validation Writing—review & editing. All authors have read and approved the final manuscript.

Funding

Open Access funding enabled and organized by Projekt DEAL. This study (01VSF16048) was funded by the innovation fund of the Federal Joint Committee (G-BA). The G-BA had no role in the design of the study; the collection, analysis, and interpretation of data; or the writing of the manuscript.

Availability of data and materials

The routine data analyzed in this study are available from the statutory health insurances TK, AOK and BARMER, but restrictions apply to the availability of the data, which were used under license for the current study and are not publicly available. To fulfill the legal requirements to obtain the data, researchers must obtain permission for a specific research question from the German Federal (Social) Insurance Office. Additionally, researchers must conclude a contract with the statutory health insurer regarding data access. The study must also be approved by the data protection officer both at the statutory health insurance and the research institute as well as the local ethics committee.

Declarations

Ethics approval and consent to participate

Permission to obtain data for the purpose of this study was granted by the German Federal (Social) Insurance Office in accordance with §75 SGB X. Further ethical approval and consent to participate were not required because the study exclusively used anonymized billing data.

Consent to publish

Not applicable.

Competing interests

JB is employed by the AOK Bundesverband, CG by the WIdO, UM by the BARMER, US and DHS by the TK and JFT by MSD (outside of this work). SF, KS, NDB and LS have nothing to declare.

Author details

[1]Technische Universität München, Uptown München Campus D, Georg-Brauchle-Ring 60/62, 80992 München, Germany. [2]Institute for Medical Information Processing, Biometry, and Epidemiology (IBE), Ludwig-Maximilians-University Munich, Munich, Germany. [3]Pettenkofer School of Public Health, Munich, Germany. [4]AOK Bundesverband, Berlin, Germany. [5]Wissenschaftliches Institut der AOK (WIdO), Berlin, Germany. [6]Techniker Krankenkasse (TK), Hamburg, Germany. [7]BARMER, Wuppertal, Germany. [8]Department of Family Medicine / General Practice, Ruhr-University Bochum, Bochum, Germany. [9]Department of Family Medicine / General Practice, Philipps-University of Marburg, Marburg, Germany.

Received: 29 April 2021 Accepted: 16 February 2022
Published online: 26 February 2022

References

1. Bundesärztekammer, Kassenärztliche Bundesvereinigung, Fachgesellschaften AdWM. Nationale VersorgungsLeitlinie Chronische KHK – Langfassung. 2014;3. Auflage (Version 1).
2. Bundesärztekammer, Kassenärztliche Bundesvereinigung, Fachgesellschaften AdWM. Nationale VersorgungsLeitlinie Chronische KHK – Langfassung. 2019; 5. Auflage (Version 1).
3. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, et al. 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J. 2020;41(3):407–77.
4. Author. [details removed for peer review]. 2013.

5. Selby JV, Fireman BH, Lundstrom RJ, Swain BE, Truman AF, Wong CC, et al. Variation among hospitals in coronary-angiography practices and outcomes after myocardial infarction in a large health maintenance organization. N Engl J Med. 1996;335(25):1888–96.
6. Niemann T, Lous J, Thorsgaard N, Nielsen TT. Regional variations in the use of diagnostic coronary angiography. A one-year population-based study of all diagnostic coronary angiographies performed in a rural and an urban Danish county. Scand Cardiovasc J. 2000;34(3):286–92.
7. Inoue T, Kuwabara H, Fushimi K. Regional variation in the use of percutaneous coronary intervention in Japan. Circ J. 2017;81(2):195–8.
8. Williams MJ, Harding SA, Devlin G, Nunn C, El-Jack S, Scott T, et al. National variation in coronary angiography rates and timing after an acute coronary syndrome in New Zealand (ANZACS-QI 6). N Z Med J. 2016;129(1428):66–78.
9. van Miltenburg-van Zijl AJ, Simoons ML, Bossuyt PM, Taylor TR, Veerhoek MJ. Variation in the use of coronary angiography in patients with unstable angina is related to differences in patient population and availability of angiography facilities, without affecting prognosis. Eur Heart J. 1996;17(12):1828–35.
10. OECD. Geographic variations in health care, OECD; 2014.
11. Kosa I, Nemes A, Belicza E, Kiraly F, Vassanyi I. Regional differences in the utilisation of coronary angiography as initial investigation for the evaluation of patients with suspected coronary artery disease. Int J Cardiol. 2013;168(5):5012–5.
12. Chew DP, MacIsaac AI, Lefkovits J, Harper RW, Slawomirski L, Braddock D, et al. Variation in coronary angiography rates in Australia: correlations with socio-demographic, health service and disease burden indices. Med J Aust. 2016;205(3):114–20.
13. Laut KG, Gale CP, Pedersen AB, Fox KAA, Lash TL, Kristensen SD. Persistent geographical disparities in the use of primary percutaneous coronary intervention in 120 European regions: exploring the variation. EuroIntervention. 2013;9(4):469–76.
14. Wennberg D, Dickens J Jr, Soule D, Kellett M Jr, Malenka D, Robb J, et al. The relationship between the supply of cardiac catheterization laboratories, cardiologists and the use of invasive cardiac procedures in northern New England. J Health Serv Res Policy. 1997;2(2):75–80.
15. Destatis. Fallpauschalenbezogene Krankenhausstatistik (DRG-Statistik) Operationen und Prozeduren der vollstationären Patientinnen und Patienten in Krankenhäusern; 2019.
16. Dissmann W, de Ridder M. The soft science of German cardiology. Lancet. 2002;359(9322):2027–9.
17. Möckel M, Searle J, Jeschke E. Indikation, Prognose und regionale Unterschiede der Herzkatheterversorgung in Deutschland (Hrsg.): Schattauer-Verlag: Stuttgart; 2014. In: Klauber J GC, Gerste B, Robra B-P, Schmacke N, editor. Versorgungs-Report 2013/2014. Stuttgart: Schattauer-Verlag; 2014.
18. Piedmont S, Swart E, Kenmogne R, Braun-Dullaeus RC. Robra BP [Left-heart catheterization followed by other invasive procedures: Regional comparisons reveal peculiar differences]. Z Evid Fortbild Qual Gesundhwes. 2017;127–128:62–71.
19. Birkmeyer JD, Reames BN, McCulloch P, Carr AJ, Campbell WB, Wennberg JE. Understanding of regional variation in the use of surgery. Lancet. 2013;382(9898):1121–9.
20. Dalhoff M. Die Regelungen zur Steuerung der gesetzlichen Krankenversicherung – eine Orientierungsanalyse –. Arbeit und Sozialpolitik. 1997;51(11/12):25–50.
21. Wennberg JE, Fisher ES, Skinner JS. Geography and the debate over medicare reform. Health Aff (Millwood). 2002;21:W96-114.
22. Chandra A, Skinner J. Technology growth and expenditure growth in health care. J Econ Lit. 2012;50(3):645–80.
23. Hartwell D, Colquitt J, Loveman E, Clegg AJ, Brodin H, Waugh N, et al. Clinical effectiveness and cost-effectiveness of immediate angioplasty for acute myocardial infarction: systematic review and economic evaluation. Health Technol Assess. 2005;9(17):1–99.
24. Jung C, Elsasser A. Update ESC guideline 2017—acute myocardial infarction (STEMI). Dtsch Med Wochenschr. 2018;143(11):797–801.
25. Gorenoi V, Schonermark MP, Hagen A. Percutaneous coronary intervention with optimal medical therapy vs optimal medical therapy alone for patients with stable angina pectoris. GMS Health Technol Assess. 2011;7:Doc07.
26. Stone GW, Hochman JS, Williams DO, Boden WE, Ferguson TB Jr, Harrington RA, et al. Medical therapy with versus without revascularization in stable patients with moderate and severe ischemia: the case for community equipoise. J Am Coll Cardiol. 2016;67(1):81–99.
27. Anselin L, Rey SJ. Modern spatial econometrics in practice: a guide to GeoDa, GeoDaSpace and PySAL. GeoDa Press LLC; 2014.
28. Ibanez B, Librero J, Bernal-Delgado E, Peiro S, Lopez-Valcarcel BG, Martinez N, et al. Is there much variation in variation? Revisiting statistics of small area variation in health services research. BMC Health Serv Res. 2009;9:60.
29. Guo HR. Age adjustment in ecological studies: using a study on arsenic ingestion and bladder cancer as an example. BMC Public Health. 2011;11:820.
30. Rosenbaum PR, Rubin DB. Difficulties with regression analyses of age-adjusted rates. Biometrics. 1984;40(2):437–43.
31. Kroll LE, Schumann M, Hoebel J, Lampert T. Regional health differences—developing a socioeconomic deprivation index for Germany. Robert Koch-Institut, Epidemiologie und Gesundheitsberichterstattung %J Journal of Health Monitoring; 2017.
32. Referenzdatenbank: Die Qualitätsberichte der Krankenhäuser [Internet]. 2017 [cited 2019]. Available from: https://g-ba-qualitaetsberichte.de/#search.
33. Anselin L, Florax RJGM. Small sample properties of tests for spatial dependence in regression models : some further results. In: Anselin L, Florax RJGM, editors. New directions in spatial econometrics. Berlin: Springer; 1995. p. 21–74.
34. Getis A, Cliff AD, Ord JK. Spatial autocorrelation. Lond Pion Progress Hum Geogr. 1973;19(2):245–9.
35. Baltagi BH, Moscone F. Health econometrics. Emerald Publishing Limited; 2018.
36. Elhorst JP. Linear spatial dependence models for cross-section data. Spatial econometrics. Springer Briefs in Regional Science. Berlin: Springer; 2014. p. 5–36.
37. Kelejian HH, Prucha IR. A generalized moments estimator for the autoregressive parameter in a spatial model. Int Econ Rev. 2001;40(2):509–33.
38. Florax R, Folmer H. Specification and estimation of spatial linear regression models: Monte Carlo evaluation of pre-test estimators. Reg Sci Urban Econ. 1992;22(3):405–32.
39. Anselin L. Lagrange multiplier test diagnostics for spatial dependence and spatial heterogeneity. Geogr Anal. 2010;20(1):1–17.
40. Leenders RTAJ. Modeling social influence through network autocorrelation: constructing the weight matrix. Soc Netw. 2002;24(1):21–47.
41. Baltagi B, Egger P, Pfaffermayr M. Estimating regional trade agreement effects on FDI in an interdependent world. J Econ. 2008;145(1–2):194–208.
42. Kelejian HH, Prucha IR. Specification and estimation of spatial autoregressive models with autoregressive and heteroskedastic disturbances. J Econ. 2010;157(1):53–67.
43. Felder S, Tauchmann H. Federal state differentials in the efficiency of health production in Germany: an artifact of spatial dependence? Eur J Health Econ HEPAC Health Econ Prev Care. 2013;14(1):21–39.
44. Boden WE, O'Rourke RA, Teo KK, Hartigan PM, Maron DJ, Kostuk WJ, et al. Optimal medical therapy with or without PCI for stable coronary disease. N Engl J Med. 2007;356(15):1503–16.
45. Rothberg MB, Sivalingam SK, Ashraf J, Visintainer P, Joelson J, Kleppel R, et al. Patients' and cardiologists' perceptions of the benefits of percutaneous coronary intervention for stable coronary disease. Ann Intern Med. 2010;153(5):307–13.
46. Kureshi F, Jones PG, Buchanan DM, Abdallah MS, Spertus JA. Variation in patients' perceptions of elective percutaneous coronary intervention in stable coronary artery disease: cross sectional study. BMJ. 2014;349:g5309.
47. Herwig A, Dehnen D, Weltermann B. Patient factors driving overuse of cardiac catheterisation: a qualitative study with 25 participants from two German teaching practices. BMJ Open. 2019;9(4):e024600.

Publisher's Note

Appendix: Additional data and sensitivity analysis

Main analysis

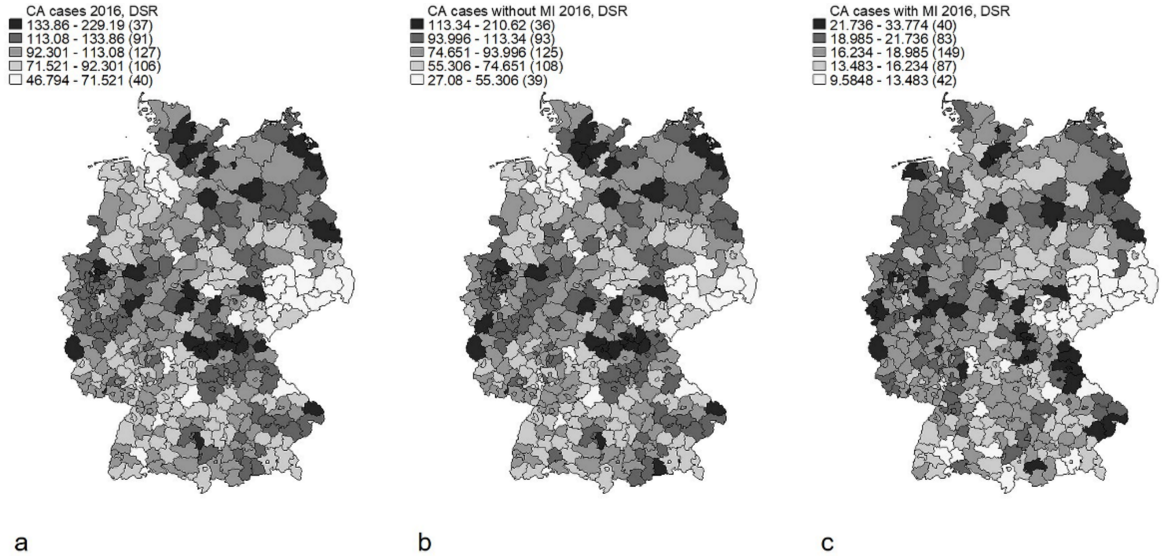

Figure A1 - Map of CA rate for (a) cases overall and (b) cases without MI (c) cases with MI, 2016; DSR, classification method: standard deviations; source: own depiction.

Table A1 – Model results of main analysis

	Cases overall				Cases without MI				Cases with MI			
	Model A (SARE)		Model B (SCRARE)		Model A (SARE)		Model B (SCRARE)		Model A (SARE)		Model B (SCRARE)	
	Wr	*We*	*Wr*	*We*	*Wr*	*We*	*Wr*	*We*	*Wr*	*We*	*Wr*	*We*
Observations	401	401	401	401	401	401	401	401	401	401	401	401
Pseudo R-squared	0.4186	0.4265	0.4261	0.4352	0.3813	0.3894	0.3895	0.3992	0.3986	0.4005	0.3995	0.4023
β (SE)												
Male under 40	185.89 (317.7)	226.79 (279.39)	221.69 (316.85)	220.09 (334.27)	110.03 (291.4)	176.18 (309.3)	141.32 (290.65)	170.21 (308.38)	41.98 (54.61)	32.46 (55.31)	43.86 (54.6)	31.17 (55.25)
Male 40 to 49	384.64 (690.36)	357.4 (685.16)	428.28 (687.63)	360.14 (715.09)	437.53 (634.6)	459.59 (662.78)	477.15 (632.15)	465.56 (660.73)	-118.57 (114.21)	-138.18 (114.61)	-118.46 (114.11)	-142.07 (114.49)
Male 50 to 59	-2024.69 (710.65)***	-2166.58 (742.87)***	-2109 (708.86)***	-2248.76 (731.19)***	-1933.22 (652.6)***	-2055.72 (675.33)***	-2009.34 (650.92)***	-2128.02 (674.8)***	-130.58 (119.5)	-139.88 (119.52)	-138.6 (119.76)	-153.38 (120.02)
Male 60 to 69	952.6 (841.23)	551.33 (1038.59)	1075.47 (839.54)	544.02 (875.41)	994.06 (773.41)	581.16 (811.5)	1108.82 (771.96)	578.01 (808.97)	3.08 (139.39)	4.93 (140.45)	9.17 (139.44)	1.47 (140.27)
Male 70 to 79	513.74 (864.64)	891.39 (1016.96)	385.25 (863.85)	755.05 (908.01)	149.08 (793.38)	565.48 (836.9)	37.41 (792.41)	443 (837.85)	243.73 (147.06)*	221.42 (148.35)	227.82 (148.1)	203.32 (149.08)
Male over 80	1727.12 (1226.06)	977.62 (1467.55)	1669.67 (1221.47)	1015.3 (1271.89)	1712.37 (1128.13)	1017.49 (1179.81)	1650.37 (1124.12)	1047.23 (1176.21)	66.65 (200.58)	27.56 (201.23)	74.85 (200.64)	40.26 (201.27)
Female 40 to 49	1345.16 (722.03)*	1329.83 (725.55)*	1389.8 (719.72)*	1311.1 (734.46)*	1121.11 (664.01)*	1100.2 (680.55)	1158.13 (661.88)*	1082.42 (678.53)	219.64 (119.03)*	224.08 (118.6)*	224.68 (119.08)*	222.01 (118.44)*
Female 50 to 59	1686.59 (851.19)**	2234.07 (931.69)**	1748.7 (847.81)**	2271.09 (892.37)**	1489.62 (780.36)*	2011.31 (825.2)**	1545.36 (777.26)**	2043.58 (822.95)**	224.61 (146.95)	240.62 (148.36)	229.38 (146.92)	246.76 (148.26)*
Female 60 to 69	-1006.93 (810.09)	-832 (947.13)	-1019.72 (806.48)	-836.8 (839.34)	-1103.98 (744.53)	-882.22 (777.6)	-1121.51 (741.22)	-891.23 (775.22)	28.18 (134.8)	9.91 (135.6)	31.43 (134.73)	14.41 (135.46)
Female 70 to 79	-368.72 (802.25)	-849.58 (941.33)	-248.38 (799.99)	-770.02 (855.93)	-102.24 (734.77)	-593.27 (789.97)	7.44 (732.69)	-519.64 (788.98)	-189.04 (141.39)	-181.01 (143.88)	-180.33 (141.6)	-173.18 (143.87)
Female over 80	-99.59 (697.38)	648.99 (825.48)	-38.35 (695.64)	691.95 (729.09)	-288.55 (641.09)	466.04 (675.73)	-235.08 (639.62)	507.65 (674.12)	23.2 (114.66)	29.87 (115.37)	24.01 (114.57)	28.88 (115.19)
Estimate of CHD prevalence[a]	10.01 (0.88)***	10.48 (1.63)***	9.87 (0.88)***	10.38 (0.88)***	8.99 (0.81)***	9.44 (0.81)***	8.87 (0.81)***	9.35 (0.81)***	1 (0.14)***	1.01 (0.14)***	0.99 (0.14)***	1 (0.14)***
GISD 2012	0.16 (0.1)	0.1 (0.11)	0.15 (0.1)	0.11 (0.1)	0.13 (0.09)	0.07 (0.09)	0.12 (0.09)	0.08 (0.09)	0.04 (0.02)**	0.04 (0.02)**	0.04 (0.02)**	0.04 (0.02)***
Cath labs[b]	40.62 (16.33)**	45.92 (19.83)**	53.41 (18.16)***	56.68 (18.32)***	37.64 (14.96)**	43.36 (15.77)***	49.34 (16.79)***	53.53 (16.95)***	2.91 (2.87)	2.97 (2.91)	3.35 (2.92)	3.49 (2.95)
W × Cath labs[b]			77.18 (47.71)	80.41 (49.84)			68.44 (44.18)	74.64 (46.56)			6.35 (7.3)	7.59 (7.14)
Constant	-143.81 (165.58)	-174.98 (142.44)	-167.02 (165.36)	-170.68 (173.94)	-103.5 (151.88)	-147.53 (160.93)	-123.82 (151.71)	-143.93 (160.46)	-20.05 (28.46)	-15.35 (28.81)	-21.27 (28.46)	-14.21 (28.78)
ρ	0.67 (0.05)***	0.72 (0.06)***	0.66 (0.05)***	0.71 (0.06)***	0.68 (0.05)***	0.72 (0.06)***	0.68 (0.05)***	0.72 (0.06)***	0.3 (0.06)***	0.31 (0.09)***	0.3 (0.06)***	0.31 (0.09)***

***p<0.01, **p<0.05, *p<0.1.
a: proportion of individuals in the total sample of insured with a confirmed diagnosis of CHD during the year 2016
b: per 10,000 population
β: regression coefficient, GISD: German Index of Social Deprivation, MI: myocardial infarction, ρ: spatial autocorrelation parameter, SE: standard error

Sensitivity Analysis

Table A2 - Frequency and characteristics of cardiac catheterization by treatment setting

	Total	Hospital		Office-based practice
		Inpatient hospital	Outpatient hospital	
Cases	n (column %)	N (row %)		
CA	425,163	369,882 (87.00%)	19,317 (4.54%)	35,964 (8.46%)
Treatment diagnosis*				
Cases with ACS	111,892 (26,31%)	109,884 (98.21%)	67 (0.60%)	1,338 (1.20%)
Cases without ACS	313,271 (73,68%)	259,998 (82.99 %)	18,647 (5.95%)	34,626 (11.05%)
Cases with stable CHD or CP	167,696 (39,44%)	125,107 (74.60 %)	15,735 (9.38%)	26,854 (16.01%)

*inpatient main hospital diagnosis, outpatient hospital diagnosis, confirmed ambulatory diagnosis in treatment case
ACS: acute coronary syndrome, CA: coronary angiography, CHD: coronary heart disease, CP: chest pain

Table A3 - Crude rate, direct standardized rate (DSR) and measures of variation

	Cases without ACS	Cases with ACS	Cases with stable CHD or CP
Crude data			
Number of CA	313,271	111,892	167,696
Crude rate per 10,000 population	75.05	26.81	40.18
Age-gender DSR in 401 districts per 10,000 population			
Median	74.15	25.78	39.65
Mean (SD)	75.45 (22.41)	26.46 (6.44)	40.13 (13.28)
Min	24.18	12.03	9.70
Max	198.53	56.11	98.00
Measures of variation			
COV	29.70	24.33	33.08
SCV	8.85	5.64	10.64

ACS: acute coronary syndrome, CA: coronary angiography, CHD: coronary heart disease, COV: coefficient of variation, CP: chest pain, DSR: direct standardized rate, SCV: systematic component of variation, SD: standard deviation

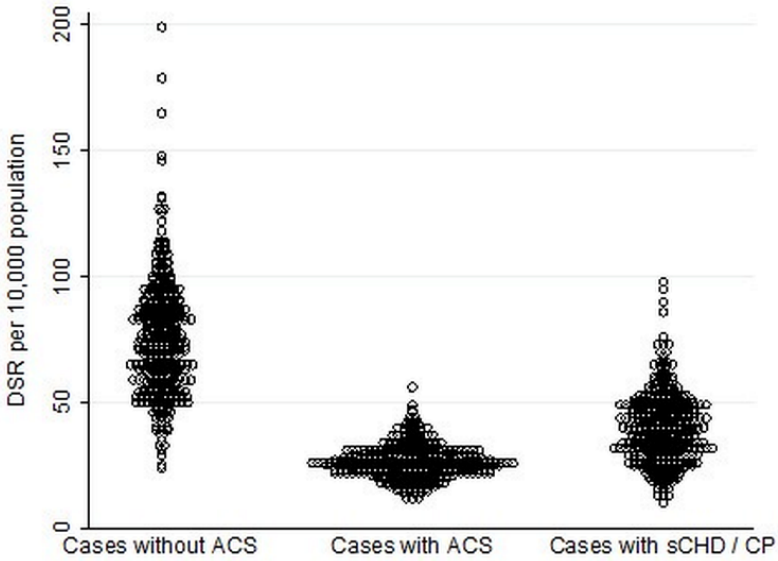

Figure A2 - Direct standardized CA rate per 10,000 population by treatment diagnosis, 2016. Each dot represents one of the 401 districts.

Appendix Table A4 – Model results of sensitivity analysis

	Cases without ACS				**Cases with ACS**				**Cases with sCHD or CP**			
	Model A (SARE)		Model B (SCRARE)		Model A (SARE)		Model B (SCRARE)		Model A (SARE)		Model B (SCRARE)	
	Wr	*We*	*Wr*	*We*	*Wr*	*We*	*Wr*	*We*	*Wr*	*We*	*Wr*	*We*
Observations	401	401	401	401	401	401	401	401	401	401	401	401
Pseudo R-squared	0.3657	0.3727	0.3763	0.3845	0.3675	0.3702	0.3678	0.3708	0.2464	0.2464	0.2505	0.2612
β (SE)												
Male under 40	63.19 (272.65)	139.54 (290.3)	96.84 (271.77)	133.36 (289.17)	91.71 (93.84)	79.76 (95.6)	92.83 (93.91)	78.88 (95.59)	193.78 (168.08)	239.41 (178.52)	212.24 (167.81)	234.75 (177.45)
Male 40 to 49	443.38 (594.76)	495.68 (622.49)	483.44 (592.05)	504.99 (620.08)	-175.12 (197.14)	-210.81 (198.64)	-174.75 (197.13)	-213.96 (198.63)	155.21 (365.51)	228.71 (381.6)	173.38 (364.38)	231.37 (379.36)
Male 50 to 59	-1511.95 (611.14)**	-1691.86 (634)***	-1587.57 (609.09)***	-1766.01 (632.88)***	-453.16 (205.86)**	-439.55 (206.72)**	-457.72 (206.45)**	-449.27 (207.77)**	-860.57 (376.13)**	-960.83 (389.44)**	-900.57 (375.53)**	-1021.7 (388.1)***
Male 60 to 69	618.55 (724.96)	283.89 (762.22)	732.93 (723.11)	286.08 (759.25)	216.88 (240.43)	157.05 (243.32)	220.76 (240.74)	153.76 (243.28)	98.96 (445.42)	-112.78 (467.12)	155.86 (444.9)	-115.09 (464.38)
Male 70 to 79	176.09 (742.52)	559.58 (785.61)	62.38 (740.89)	434.24 (785.72)	266.21 (253.05)	280.09 (256.59)	257.45 (254.96)	266.66 (258.13)	192.23 (457.51)	471.04 (482.76)	127.09 (457.53)	373.08 (481.98)
Male over 80	1568.07 (1058.14)	859.85 (1108.54)	1500.74 (1053.72)	884.51 (1104.34)	283.65 (346.52)	229.45 (348.99)	287.53 (346.8)	238.99 (349.37)	1093.08 (649.36)*	811.32 (678.3)	1062.11 (647.42)	834.74 (674.49)
Female 40 to 49	849.2 (622.56)	829.17 (639.14)	888.32 (620.07)	809.2 (636.74)	498.01 (205.46)**	507.68 (205.35)**	500.75 (205.71)**	506.41 (205.3)**	755.97 (382.34)**	662.18 (391.92)*	781.57 (381.41)**	647.8 (389.66)*
Female 50 to 59	1167.86 (729.84)	1717.64 (774.38)**	1227.97 (726.41)*	1749.62 (771.52)**	522.09 (252.46)**	539.12 (256.34)**	524.83 (252.64)**	543.84 (256.45)**	895.89 (450.26)**	1239.65 (476.55)***	927.9 (448.97)**	1265.8 (473.8)***
Female 60 to 69	-636.89 (697.7)	-491.73 (730.2)	-651.84 (694.07)	-505.5 (727.37)	-291.95 (232.46)	-256.19 (234.85)	-290.56 (232.52)	-252.38 (234.86)	44.97 (428.88)	38.8 (448.01)	43.92 (427.33)	35.31 (445.35)
Female 70 to 79	-113.45 (686.7)	-541.33 (741.15)	-2.07 (684.27)	-463.41 (739.5)	-269.16 (242.27)	-310.4 (248.29)	-264.06 (242.86)	-304.84 (248.57)	-216.9 (424.23)	-455.83 (456.58)	-159.66 (423.55)	-397.68 (454.55)
Female over 80	-343.78 (600.84)	417.81 (634.82)	-284.99 (599.09)	462.87 (632.86)	73.33 (198.1)	93.3 (200.16)	74.06 (198.11)	92.78 (200.06)	-147.18 (369.24)	193.36 (388.67)	-113.96 (368.64)	225.32 (386.67)
Estimate of CHD prevalence[a]	7.82 (0.76)***	8.26 (0.76)***	7.7 (0.76)***	8.16 (0.76)***	2.13 (0.24)***	2.16 (0.24)***	2.12 (0.24)***	2.15 (0.24)***	3.94 (0.46)***	4.07 (0.47)***	3.88 (0.47)***	4 (0.46)***
GISD 2012	0.08 (0.09)	0.03 (0.09)	0.07 (0.09)	0.04 (0.09)	0.08 (0.03)***	0.08 (0.03)***	0.08 (0.03)***	0.08 (0.03)***	0.06 (0.05)	0.06 (0.05)	0.06 (0.05)	0.07 (0.05)
Cath labs[b]	37.72 (13.99)***	43.42 (14.79)***	50.44 (15.8)***	54.07 (15.93)***	2.67 (4.93)	3.04 (5.01)	2.95 (5.03)	3.47 (5.1)	15.43 (8.64)*	19.08 (9.12)**	21.93 (9.64)**	26.6 (9.71)***
W × Cath labs[b]			72.23 (41.62)*	77.58 (43.97)*			3.56 (12.69)	5.75 (12.45)			38.53 (25.33)	56.98 (26.32)**
Constant	-83.54 (142.11)	-131.65 (151.04)	-105.32 (141.86)	-128.09 (150.45)	-41.26 (48.9)	-36.15 (49.78)	-41.99 (48.96)	-35.35 (49.8)	-124.5 (87.6)	-148.23 (92.89)	-136.39 (87.59)	-145.17 (92.34)
ρ	0.68 (0.05)***	0.72 (0.05)***	0.68 (0.05)***	0.71 (0)***	0.34 (0.07)***	0.36 (0.1)***	0.34 (0.07)***	0.36 (0.1)***	0.63 (0.05)***	0.68 (0.06)***	0.63 (0.05)***	0.67 (0.06)***

***p<0.01, **p<0.05, *p<0.1.
a: proportion of individuals in the total sample of insured with a confirmed diagnosis of CHD during the year 2016
b: per 10,000 population
β: regression coefficient, GISD: German Index of Social Deprivation, MI: myocardial infarction, ρ: spatial autocorrelation parameter, SE: standard error

4. Paper 2

Open access | Original research

BMJ Open

Use of guideline-recommended drug therapy in patients undergoing percutaneous coronary intervention for stable coronary heart disease in Germany: a multilevel analysis of nationwide routine data

Julia Frank-Tewaag [1,2,3] Julian Bleek,[4] Dirk Horenkamp-Sonntag,[5] Ursula Marschall,[6] Uwe Zeymer,[7] Norbert Donner-Banzhoff,[8] Leonie Sundmacher[9]

To cite: Frank-Tewaag J, Bleek J, Horenkamp-Sonntag D, *et al*. Use of guideline-recommended drug therapy in patients undergoing percutaneous coronary intervention for stable coronary heart disease in Germany: a multilevel analysis of nationwide routine data. *BMJ Open* 2020;**10**:e042886. doi:10.1136/bmjopen-2020-042886

► Prepublication history and additional materials for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2020-042886).

Received 17 July 2020
Revised 15 September 2020
Accepted 25 November 2020

Check for updates

For numbered affiliations see end of article.

Correspondence to
Julia Frank-Tewaag;
J.FrankTewaag@lmu.de

ABSTRACT

Objectives To determine the prescription of guideline recommended drug therapy in patients with stable coronary heart disease (sCHD) prior to percutaneous coronary intervention (PCI) in Germany and to examine the role of patient characteristics and features of regional healthcare supply in a multilevel model.

Design Secondary data analysis of factors associated with the prescription of guideline recommended drug therapy using a multilevel model to analyse regional-level effects, over and above the effects of patient-level demographic and health status.

Setting Office-based prescriptions in the year prior to the invasive procedure.

Participants A linked nationwide dataset from Germany's three largest statutory health insurance funds of all patients receiving PCI in the year 2016.

Main outcome measures Patients' odds of receiving optimal medical therapy and symptom-oriented therapy within 1 year prior to PCI.

Results 68.6% of patients received at least one lipid-lowering drug and one symptom-oriented therapy prior to PCI. 43.6% received at least two agents to control their symptoms. Patients who received treatment in accordance with the recommendations had a greater number of diagnosed risk factors, a more severe history of cardiac disease and used a higher volume of ambulatory office-based physician services. The prescriptions prevalence for the symptom-oriented therapies differed significantly between eastern and western Germany, with a higher prevalence in the eastern districts.

Conclusions Guidelines can only provide decision-making corridors, and the applicability of recommendations must always be assessed on a case by case basis. Nevertheless, our analysis indicates that the prevalence of prescriptions in routine practice is subject to substantial variation and that conservative therapy options are not fully exhausted prior to PCI. This suggests that there might be room for improvement in the care of patients with sCHD.

Strengths and limitations of this study

- ► We used a linked, comprehensive, nationwide data set with patient-level information on prescriptions, hospital and ambulatory care from the three largest statutory health insurers in Germany, covering approximately 42.5 million individuals.
- ► We examined the role of the health care supply and regional characteristics, in addition to patient-level demographic and health status variables, on the prescription guideline recommended drug therapy.
- ► The large number of patients examined in the analysis allowed us to generate reliable estimates on the regional level.
- ► The prescription data do not include drugs prescribed and administered in hospitals and of over-to-counter drugs.
- ► Because a prescription was recorded only in cases where a patient redeemed it, a low prescription prevalence may be due to poor implementation of treatment recommendations on the part of providers or a lack of adherence or treatment discontinuation on the part of patients.

BACKGROUND

In addition to lifestyle-modifying measures, drug therapy has become the mainstay of treatment in patients with stable coronary heart disease (sCHD). Comprehensive meta-analyses,[1 2] the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) study[3] and the recent landmark International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial[4 5] provide strong evidence that coronary revascularisation is not associated with an improvement of the prognosis compared with optimal drug therapy in this patient group. Current clinical guidelines recommend drug therapy as the initial approach to managing patients with sCHD, with percutaneous coronary intervention (PCI) reserved for patients whose symptoms persist despite optimal medical therapy (OMT).[6–8]

The translation of these findings and recommendations into clinical practice, however, might be a subject for improvement. Studies in the USA[9] and Canada[10] looked at large samples of patients with sCHD who underwent elective PCI, and therefore, should generally have received drug therapy before this invasive intervention. They found, however, that the proportion of individuals in whom that had indeed been the case was disappointingly small. The authors of the Canadian study suggested several explanations for their findings, including an overestimation of the benefits of PCI among patients, the non-universal acceptance by doctors of the results of recent trials, or knowledge gaps among clinicians regarding appropriate management of patients with sCHD.[10] According to a health technology assessment report by Gorenoi *et al*, about two-thirds of PCIs are unnecessary because the symptoms could also be managed in a conservative manner using drug therapy.[11] While there have been no equivalent studies of patients who underwent PCI in Germany, researchers have investigated the use of drug therapy after hospitalisation or after acute cardiovascular events[12–17] and found that it has been suboptimal in patient groups that would have benefited from it according to current treatment guidelines.

The aim of the present study is to contribute to this evidence base by drawing on a nationwide set of routine healthcare data to assess whether patients who underwent PCI received guideline-recommended drug therapy during the year before they underwent the invasive procedure. To do so, we obtained and linked nationwide data from three large statutory health insurers (SHIs). First, we examined whether clinical practice in Germany reflects the recommendations of the German and European guidelines among patients with sCHD and if there might be opportunities to improve their care. Subsequently, we estimated a multilevel model to examine the influence of patient characteristics, and the supply of healthcare services in different geographies, on the use of drug therapy because the literature suggests that both can play an important role in this regard.[16 18–30]

METHOD

Database

Our analysis was based on a set of linked billing data from the SHIs AOK, BARMER and Techniker Krankenkasse from the years 2014–2016. The dataset comprises patients who underwent PCI in 2016 as an inpatient, outpatient or in an office-based practice. We supplemented the dataset with the anatomical therapeutic chemistry (ATC) classification by linking it to the WIdO database of pharmaceutical products.[31] Moreover, we added the characteristics of regional healthcare supply from the INKAR database[32] and the National Association of Statutory Health Insurance Physicians (Kassenärztliche Bundesvereinigung, KBV).[32 33]

Patient population

We included patients in the study if they were 18 years of age or older and had received PCI in 2016 as an inpatient, an outpatient or in an office-based practice (EBM: 34292, OPS: 8–837). To limit the population to individuals with sCHD, our main analysis included only patients treated for chronic ischaemic heart disease (I25), stable angina pectoris (I20.8 and I20.9) or chest pain (R07) at the time of PCI. To avoid any impact from recent coronary events, we excluded all patients who had undergone PCI or coronary artery bypass graft surgery (CABG) in 2015 or had had an acute myocardial infraction (MI) within the year before the index PCI. Furthermore, we considered only those patients who had been insured for at least 360 days in the years before the index PCI and without missing information. Patients who died during or after the PCI were not excluded.

In addition, to assess possible differences in the prescription prevalence depending on the indication, we undertook a sensitivity analysis (1) that included patients with unstable angina pectoris (I20.0 and I20.1). The main analysis comprised patients who had an inpatient or office-based diagnosis of CHD (ICD I20–I25, inpatient primary or secondary diagnosis or confirmed office-based diagnosis in at least two quarters) during the period from 2014 to the billing quarter prior to the index PCI. This restriction presupposes that patients had contact with inpatient medical services at least once or had seen an office-based physician more than once. Therefore, in a second sensitivity analysis (2), we examined patients without a confirmed diagnosis of CHD in the observation period.

Prescription prevalence and measures of guideline-concordant care

Our analysis considers the recommendations of both the German and European guidelines on the management of sCHD.[6–8] Using data on prescriptions, we divided patients into users and non-users of the recommended drug therapies in the year before PCI using the ATC classification (see online supplemental file 1, table 1 for the ATC codes is used). Lastly, we grouped the classes of substances, according to the guideline recommendations, as preferred or alternative treatments and classified these as having been prescribed with the aim of improving a patient's prognosis or relieving his or her symptoms. For the purpose of our analysis, we considered beta-blockers as belonging to the latter of these categories even though they can also enhance prognosis (see figure 1).

Based on these classifications, we defined 'OMT' as a combined measure that reflected the guideline recommendations. For this measure, we defined a patient as a user if, within the year before PCI, he or she had had received at least one prescription for a lipid-lowering

Table 1 Individual characteristics and prescription prevalence

		Optimal medical therapy*		Symptom-oriented therapy†		
	Total (n=22551) n, (%)	Criterion fulfilled (n=15473) n, (%)	P value	At least one (n=9805) n, (%)	At least two (n=9824) n, (%)	P value
Under 50 years	300 (1.33)	220 (73.33)	<0.001	148 (49.33)	99 (33)	<0.001
50–59 years	2100 (9.31)	1468 (69.9)		1061 (50.52)	693 (33)	
60–69 years	5081 (22.53)	3636 (71.56)		2229 (43.87)	2125 (41.82)	
70–79 years	9803 (43.47)	6756 (68.92)		4258 (43.44)	4296 (43.82)	
Over 80 years	5267 (23.36)	3393 (64.42)		2109 (40.04)	2611 (49.57)	
Male	16381 (72.64)	11302 (68.99)	0.04	7317 (44.67)	6752 (41.22)	<0.001
Female	6170 (27.36)	4171 (67.6)		2488 (40.32)	3072 (49.79)	
No participation in DMP CHD	13052 (57.88)	8289 (63.51)	<0.001	5739 (43.97)	5325 (40.8)	<0.001
Participation in DMP CHD	9499 (42.12)	7184 (75.63)		4066 (42.8)	4499 (47.36)	
No prior MI	13753 (60.99)	8669 (63.03)	<0.001	5846 (42.51)	5815 (42.28)	<0.001
Prior MI	8798 (39.01)	6804 (77.34)		3959 (45.00)	4009 (45.57)	
No PCI or CABG	20003 (88.7)	13546 (67.72)	<0.001	8667 (43.33)	8694 (43.46)	0.007
Prior PCI or bypass	2548 (11.3)	1927 (75.63)		1138 (44.66)	1130 (44.35)	
No heart failure	14956 (66.32)	10008 (66.92)	<0.001	6573 (43.95)	6145 (41.09)	<0.001
Heart failure	7595 (33.68)	5465 (71.96)		3232 (42.55)	3679 (48.44)	
No hypertension	1486 (6.59)	782 (52.62)	<0.001	720 (48.45)	281 (18.91)	<0.001
Hypertension	21065 (93.41)	14691 (69.74)		9085 (43.13)	9543 (45.3)	
No lipid metabolism disorder	4253 (18.86)	2066 (48.58)	<0.001	1926 (45.29)	1626 (38.23)	<0.001
Lipid metabolism disorder	18298 (81.14)	13407 (73.27)		7879 (43.06)	8198 (44.8)	<0.001
No diabetes mellitus	11665 (51.73)	7572 (64.91)	<0.001	5302 (45.45)	4499 (38.57)	<0.001
Diabetes mellitus	10886 (48.27)	7901 (72.58)		4503 (41.37)	5325 (48.92)	
No PAD	19054 (84.49)	12880 (67.6)	<0.001	8445 (44.32)	8081 (42.41)	<0.001
PAD	3497 (15.51)	2593 (74.15)		1360 (38.89)	1743 (49.84)	
No dementia	21391 (94.86)	14735 (68.88)	<0.001	9319 (43.57)	9287 (43.42)	0.133
Dementia	1160 (5.14)	738 (63.62)		486 (41.9)	537 (46.29)	
No depression	17387 (77.1)	12033 (69.21)	<0.001	7623 (43.84)	7525 (43.28)	0.129
Depression	5164 (22.9)	3440 (66.62)		2182 (42.25)	2299 (44.52)	
Low use of office-based services‡	6097 (27.04)	3869 (63.46)	<0.001	2638 (43.27)	2403 (39.41)	<0.001
GP or primary care internist	5861 (25.99)	3828 (65.31)		2525 (43.08)	2583 (44.07)	
Cardiologist	10593 (46.97)	7776 (73.41)		4642 (43.82)	4834 (45.67)	
No ASA/clopidogrel	11850 (52.55)	7240 (61.1)	<0.001	5188 (43.78)	4770 (40.25)	<0.001
ASA/clopidogrel	10701 (47.45)	8233 (76.94)		4617 (43.15)	5054 (47.23)	
No ACE/ARB	4546 (20.16)	2295 (50.48)	<0.001	1994 (43.86)	1298 (28.55)	<0.001
ACE/ARB	18005 (79.84)	13178 (73.19)		7811 (43.38)	8526 (47.35)	
No molsidomine	20967 (92.98)	14226 (67.85)	<0.001	9380 (44.75)	8742 (41.69)	<0.001
Molsidomine	1584 (7.02)	1247 (78.72)		425 (26.83)	1082 (68.31)	
No diuretics	9828 (43.58)	6112 (62.19)	<0.001	4511 (45.9)	3366 (34.25)	<0.001
Diuretics	12723 (56.42)	9361 (73.58)		5294 (41.61)	6458 (50.76)	
No polymedication§	6095 (27.03)	3004 (49.29)	<0.001	3225 (52.91)	1399 (22.95)	<0.001
Polymedication§	16456 (72.97)	12469 (75.77)		6580 (39.99)	8425 (51.20)	

Continued

Table 1 Continued

	Total (n=22 551) n, (%)	Optimal medical therapy* Criterion fulfilled (n=15 473) n, (%)	P value	Symptom-oriented therapy† At least one (n=9805) n, (%)	At least two (n=9824) n, (%)	P value

*At least one lipid-lowering and one symptom-oriented therapy.
†At least two classes of drugs or combination.
‡Patients with fewer than two visits to a physician per year.
§Patients with more than five long-term (DDD lasting for 90 days or more) prescriptions according to ATC code.
ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blockers; ASA, acetylsalicylic acid; ATC, Anatomical Therapeutic Chemistry; CABG, coronary artery bypass graft; CHD, coronary heart disease; DMP, disease management program; GP, general practitioner; MI, myocardial infraction; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention.

agent (ie, a statin, fibrate, anion exchanger or cholesterol absorption inhibitor) and at least one prescription for a recommended symptomatic therapy (ie, a beta-blocker, calcium channel blocker, ivabradine, ranolazine or organic nitrate).

Because (1) the prescription prevalence of antiplatelet agents could not be reliably estimated due to the over-to-counter (OTC) availability of acetylsalicylic acid (ASA), (2) molsidomine is not recommended as an alternative to nitrates and (3) the indication for the use of angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARB) could not be clearly derived, we did not consider the use of these agents in our analysis of the two combined measures. We do, however, present the prescription prevalence of these and of other active substances with intersecting indications descriptively.

Because the symptomatic relief of chest pain plays an important role, especially when PCI is considered as a subsequent treatment option, we examined symptom-oriented therapy alone in a separate analysis and paid special attention to whether the options for conservative treatment had been exhausted. For this purpose, we classified patients as users if they received a prescription for at least two classes of symptom-oriented therapy within the year before PCI.

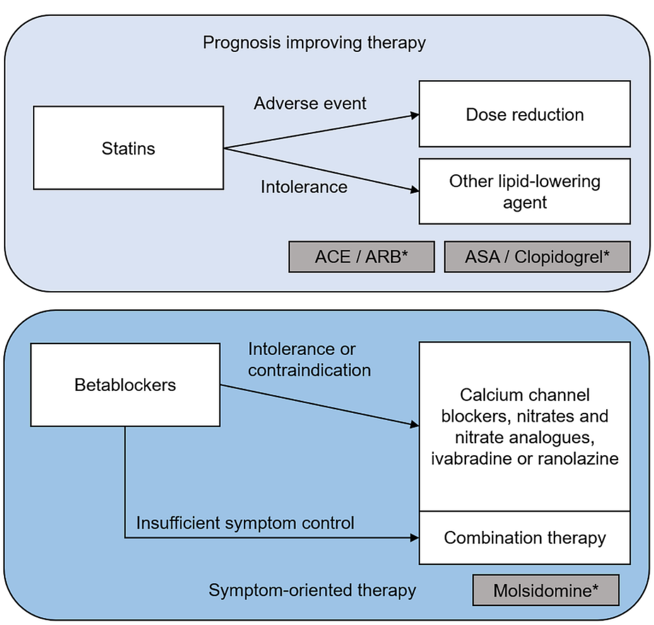

Figure 1 Systematisation of drug therapy based on guideline recommendations. For the purpose of our analysis, beta-blockers were considered as belonging to the symptom-oriented therapy. *Not included in the combined endpoints. ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blockers; ASA, acetylsalicylic acid.

Study variables

There are many reasons why patients may fail to receive a recommended drug therapy or not follow a recommended regimen. Obstacles can exist at the level of the patient, the provider and the health system. We, therefore, undertook a multilevel analysis to examine how patient-specific and regional health services supply factors might affect the use of the recommended drug therapies. In doing so, we considered factors for which there is evidence of an association with poor use of guideline-recommended drug therapies or high rates of treatment discontinuation[16 18–30] (see online supplemental file 2, for the description of the variable selection and table 1 for the International Classification of Diseases, 10th Revision,German Modification (ICD-10-GM) codes that were used).

Statistics

We presented prescription prevalence in a descriptive manner. The patient characteristics were stratified according to drug therapy and compared using χ^2 test. In a logistic regression model, we examined the influence of patient-specific study variables on prescription prevalence. Subsequently, within a multilevel model, we considered variation at the level of the administrative districts and examined the influence of the variables related to features of local healthcare supply. For the purpose of multilevel analysis, we mean centred age. We assessed the specific and general context effects by intraclass correlation coefficient (ICC), median OR (MOR), proportion change in variance (PCV), proportion of opposite odds (POOR), 80%-interval OR (80%-IOR) and ROC AUC curve comparisons. We considered a $p<0.05$ to be statistically significant. Analyses were performed with StataSE V.15.

Patient and public involvement

Patients and public were not involved.

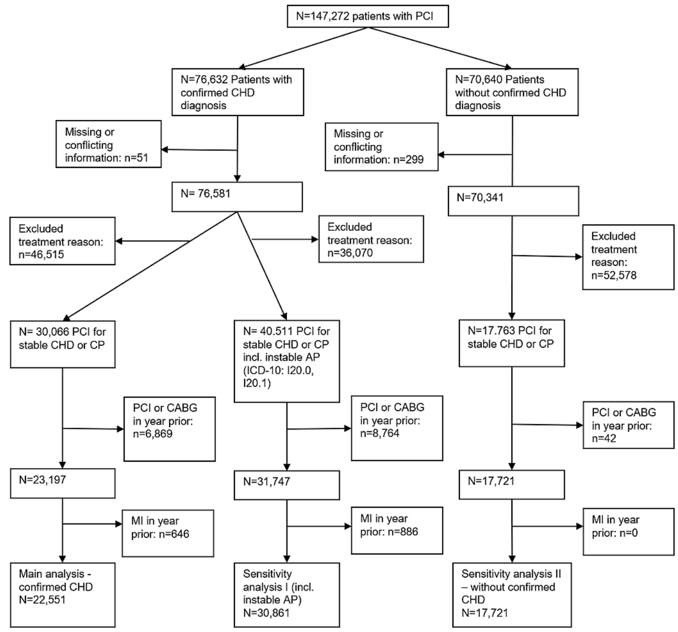

Figure 2 Selection of the patient population. AP, angina pertoris; CABG, coronary artery bypass graft; CHD, coronary heart disease; CP, chest pain; ICD, International Classification of Diseases; MI, myocardial infarction; N, number of patients; PCI, percutaneous coronary intervention.

RESULTS

Study sample

The dataset comprised nationwide linked billing data from approximately 42.5 million individuals. In 2016, a total of 147 272 patients in the dataset received at least one PCI. The selection yielded a study population for the main analysis consisting of 22 551 patients. In addition, we performed a sensitivity analysis (1) including patients with unstable angina pectoris and a further sensitivity analysis (2) with patients who did not have a confirmed CHD diagnosis prior to the index PCI (see figure 2).

Prescription prevalence

Within the year before the index PCI in 2016, the criterion of OMT was met in 68.61% of patients. 25.40% were prescribed only one of these therapies, and 5.99% received no OMT-prescriptions. Of the 17 044 (75.58%) patients who received a prescription for a lipid-lowering drug, the majority (98.04%) were prescribed a statin. Of the 19 629 (87.04%) patients who received a prescription for at least one of the symptom-oriented therapies, 43.56% were prescribed at least two symptom-oriented drugs. The majority of patients received a prescription for a beta-blocker (75.36%), 33.87% a prescription for a calcium channel blocker and 26.02% a prescription for a regimen consisting of both agents. 26.47% were prescribed an organic nitrate. Ivabradine was prescribed in fewer than 2%, ranolazine in just over 5% of patients (see figure 3 and table 1 for individual characteristics and prescription prevalence).

Sensitivity analysis including patients with unstable angina pectoris revealed minor differences in prescription prevalence. Patients without a confirmed diagnosis of CHD prior to PCI had a lower prescription prevalence for all drug classes. The criterion of OMT was fulfilled in 31.13% of these patients. Seventy-six per cent received a prescription for at least one of the two therapies, and 24.00% receive no OMT-prescriptions. 63.81% of the patients received a prescription for at least one of the symptom-oriented therapies, and 24.07% of the patients

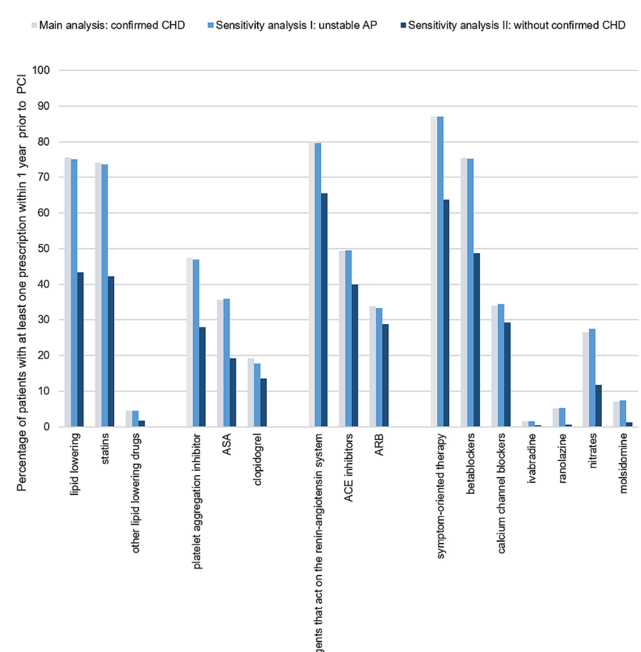

Figure 3 Prescription prevalence of the active substances. Percentage of patients with at least one prescription within 1 year prior to PCI. ACE, angiotensin-converting enzyme; AP, angina pertoris; ARB, angiotensin II receptor blockers; ASA, acetylsalicylic acid; CHD, coronary heart disease; PCI, percutaneous coronary intervention.

received a prescription for at least two classes of these drugs.

Optimal medical therapy

Patients with a previous MI, a diagnosed lipid metabolism disorder, previous CABG or PCI, diabetes mellitus, PAD, heart failure or hypertension had higher odds of receiving the OMT within the year before the index PCI (see table 2). Above average age and a diagnosis of dementia or depression were associated with lower odds of receiving a prescription for the OMT. The sex of the patient showed no significant association with such prescriptions. Although symptom-oriented therapy was prescribed more frequently in women, the proportion of men who were prescribed a lipid-lowering drug was 76.54% compared with 73.03% in women (p<0.001). Participation in a disease management program (DMP) for CHD was associated with a higher odds of being prescribed the OMT. Patients who made at least two visits to the general practitioner (GP) or primary care internist per year or who had an additional contact with a cardiologist had higher odds of being prescribed the OMT or primary care internist per year or who had an additional contact with a cardiologist had higher odds of being prescribed the OMT compared with patients who made fewer visits. The variables at the regional level showed no statistically significant effect. Although likelihood-ratio tests suggest that the differences between the districts is not zero, the ICC points to a low correlation within each of the districts. The measures of the general and specific context effects suggest that the variables characterising the regional healthcare supply had little explanatory power and accounted for only a small proportion (PCV=4.9%) of variance at the district level.

Symptom-oriented therapy

Prior MI, above average age, female gender and diagnosed risk factors and comorbidities, were associated with a higher odds of receiving a prescription for symptom-oriented therapy in the year before the index PCI. Enrolment in a DMP for CHD, regular visits to the GP or primary care internist and additional contact with a cardiologist also showed a positive association compared with patients who used fewer healthcare services. A previous PCI or CABG, or a diagnosis of dementia or depression showed no significant influence on such prescriptions. The variables we considered for regional healthcare supply also showed no significant association. However, patients in eastern Germany had higher odds of being prescribed symptom-oriented therapy after considering patient characteristics. The comparison of eastern and western German districts suggests that there is, on average, a positive association for the former, with an OR of 1.19 (95% CI 1.09 to 1.30). However, unmodelled interdistrict variability remained, which is reflected in the broad 80% IOR(95% CI 0.86 to 1.64). The POOR was moderate (24.5%). The model, including the regional variables, explains 14.20% of the variance at district level.

Table 2 Multilevel model of influencing factors

	Optimal medical therapy†		Symptom-oriented therapy‡	
	OR	95% CI	OR	95% CI
Individual level				
Age§	0.99	(0.98 to 0.99)**	1.01	(1.01 to 1.02)**
Female	1.06	(0.99 to 1.13)	1.37	(1.29 to 1.46)**
DMP CHD	1.58	(1.49 to 1.69)**	1.23	(1.17 to 1.31)**
Prior MI	1.71	(1.60 to 1.82)**	1.13	(1.07 to 1.20)**
Previous PCI/ CABG	1.23	(1.11 to 1.36)**	1.01	(0.92 to 1.10)
Heart failure	1.08	(1.01 to 1.15)*	1.13	(1.07 to 1.20)**
Hypertension	1.66	(1.48 to 1.86)**	2.8	(2.44 to 3.21)**
Lipid metabolism disorder	2.46	(2.29 to 2.64)**	1.15	(1.07 to 1.24)**
Diabetes mellitus	1.34	(1.26 to 1.42)**	1.38	(1.30 to 1.46)**
PAD	1.22	(1.12 to 1.33)**	1.23	(1.14 to 1.32)**
Dementia	0.75	(0.66 to 0.86)**	0.89	(0.78 to 1.00)
Depression	0.81	(0.76 to 0.88)**	0.97	(0.90 to 1.03)
GP or primary care internist	1.17	(1.08 to 1.27)**	1.16	(1.08 to 1.26)**
Cardiologist	1.47	(1.37 to 1.59)**	1.19	(1.11 to 1.27)**
District level				
Pharmacies per 100 000 inhabitants	1	(0.99 to 1.01)	1.01	(1.00 to 1.02)
GPs per 100 000 inhabitants	1	(0.99 to 1.01)	1	(0.99 to 1.00)
Internists per 100 000 inhabitants	1	(1.00 to 1.01)	1	(1.00 to 1.01)
No of cases per GP	1	(1.00 to 1.00)	1	(1.00 to 1.00)
No of cases per internist	1	(1.00 to 1.00)	1	(1.00 to 1.00)
Eastern Germany	1.01	(0.91 to 1.11)	1.19	(1.09 to 1.30)**
Constant	0.28	(0.18 to 0.43)**	0.12	(0.08 to 0.17)**
Variance of districts	0.04	(0.02 to 0.06)	0.03	(0.02 to 0.05)

*P<0.05, **p<0.001.
†At least one lipid-lowering and one symptom-oriented therapy.
‡At least two classes of drugs or combination.
§Mean centred.
CABG, coronary artery bypass graft surgery; CHD, coronary heart disease; DMP, disease management program; GP, general practitioner; MI, myocardial infraction; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention.

Considering the patient characteristics and the multilevel structure, the MOR is 1.20, or 1.18 if the district variables are included—that is, if a person moves to another district with a higher prescription likelihood, their risk of getting a prescription in median increases 1.20 or 1.18 times.

DISCUSSION

Using a comprehensive set of nationwide routine data, the present study is the first to analyse patterns of use of guideline-recommended drug therapies among patients with sCHD in Germany in the time before they undergo PCI. The study also explores the association of these patterns with characteristics of regional healthcare supply and patient characteristics.

Although the European and German guidelines[6–8] recommend drug therapy in patients with sCHD, our findings suggest that the recommendations are only fulfilled to a moderate degree that and there is substantial variation in how they are being implemented in Germany. In general, patients in our sample who received treatment in accordance with these recommendations were those who had a greater number of diagnosed risk factors and comorbidities and a more severe history of cardiac disease compared with patients who did not.

The associations observed in our analysis are consistent with the results of the Canadian study except that Garg *et al* observed a weak positive association in men.[10] While we found that the use of symptom-oriented therapy in women was more frequent, gender showed no significant association with the OMT. This can be attributed to the lower prescription prevalence of statins in women in our sample, which is consistent with the results of a study on secondary prevention in CHD in Germany[34] and with the findings of the EUROASPIRE IV and V surveys.[13 17] We found that patients with diagnosed depression, above average age and diagnosed dementia have lower odds of receiving the OMT. It might, therefore, be useful to pay special attention in consultations with these patients when discussing, reviewing and agreeing on individual treatment plans.

The volume of ambulatory office-based services used by patients and of care provided by GPs and additional visits to cardiologists showed a positive association with the prescription of OMT. However, the variables included at the district level showed no discernible influence on the prevalence of OMT prescriptions.

The prevalence of prescriptions for the symptom-oriented therapies differed significantly between eastern and western Germany, with a higher prevalence in the eastern districts. These results are consistent with those found in a study in patients with heart failure, which also suggest an east-west gradient in the use of beta-blocker therapy.[35] These differences could be due to several factors, such as different patient preferences, historical differences in service providers' experience, preferences regarding the prescription, differences in drug budgets or variations in the market penetration of certain drugs. The role of the physician in the implementation of prevention guidelines for CHD and barriers to their implementation was studied by Reiner *et al*. The authors found that, although most physicians believe that guidelines are useful and necessary, 11.9% of primary care physicians, 7.0% of internists and 4.8% of cardiologists prefer to rely on their own personal experience.[36] Moreover, the frequency of PCI varies widely within Germany,[37–39] which suggests that the observed differences might reflect varying preferences in the use of invasive therapies.

Looking at patients regardless of whether they had a confirmed diagnosis of CHD, we found a prescription prevalence for most drug classes that was lower than that seen by Borden *et al* in the USA and Garg *et al* in Canada, with the exception of ACE inhibitors/ARB and beta-blockers.[9 10] In the USA, 62.6% of these patients received a beta-blocker compared with 56.9% in Canada and 63.61% in Germany. While 64.3% of patients in Canada and the USA received a statin, the percentage in Germany was 60.10%. Compared with the Canadian study, the proportion of patients receiving prescriptions was lower by 6.94% for calcium channel blockers, 3.45% for nitrates. It should be noted, however, that the observation period for measuring prescription prevalence in the two other studies was shorter than in ours, the composition of their patient sample may have differed and the combined measures they used are not directly comparable to those used in our analysis because they are based on different definitions.

The EUROASPIRE cross-sectional surveys have evaluated guideline implementation in European countries and found that, a large majority of patients with documented CHD, fail to achieve the therapeutic targets. When comparing the most recent results for Germany with those for patients with known CHD in our study, we find that the proportion of patients receiving lipid lowering medication was 12% lower in our analysis than the proportion reported in EUROASPIRE V[17] and the proportion receiving statins 7% lower compared with EUROASPIRE IV.[13] Similarly the prescription prevalence we found for beta-blockers and for ACE inhibitors/ARB was lower than the proportion reported for Germany in EUROASPIRE IV, by 8% and 2%, respectively. It should be noted, however, that the patient's sample of the EUROASPIRE surveys differs to the one in our analysis, because patients with documented CHD were recruited following hospitalisation. Zhao *et al*[40] have investigated medication use in patients with documented CHD in Europe, Asia and the Middle East and found substantial variations between regions and countries. The proportion of medication use the authors reported for Europe were higher than those found in our study with exception of calcium antagonist and ARBs. Again, it has to be noted that the patient sample differs to the one in our study, because participants were recruited from cardiology outpatient clinics in participating centres.

Because the results of our study may be considered as real-world evidence reflecting current routine practice, as opposed to observations made in clinical trials with strict control of drug regimens and selected patient populations, it is not surprising that the medication use reported after 5 years in the COURAGE study[41] and after 1 year in the ISCHEMIA trial[42] were higher than the prescription prevalence found in our analysis.

LIMITATIONS

This study has several important limitations. First, our prescription data do not include drugs prescribed and administered in hospitals,[43] which could lead to an underestimation of prescription prevalence. Second, because we could not rule out the OTC use of ASA, we expected the prevalence of its use to be underestimated.[44] Third, because prescription data in Germany are passed on from the pharmacies to health insurers, a prescription was recorded only in cases where a patient redeemed it. Thus, a low prescription prevalence may be due to poor implementation of treatment recommendations on the part of providers or a lack of adherence or treatment discontinuation on the part of patients. Fourth, the drug therapies included in our model are not disease specific, and physicians' decisions to prescribe them may have been influenced by patients' comorbidities. This can lead to an overestimation of the prescription prevalence attributable to the CHD diagnosis. Fifth, our analysis does not consider intolerance or contraindications. Although we take account of the fact that the guidelines recommend alternatives, we cannot exclude the possibility that in certain cases both the preferred and alternative therapies were not prescribed because both were contraindicated. Sixth, the coding behaviour of physicians influences the documented diagnoses and there may be regional and specialty-specific differences in the coding. This can lead to a misclassification of patients in the study sample and subgroups. Lastly, our model does not consider the supply of care in surrounding districts and therefore only allows conclusions to be drawn about the impact of healthcare supply in a patient's district of residence. If care supply for the surrounding districts plays an important role, this will not be reflected in our findings.

CONCLUSION

The present analysis is the first to provide insights into the patterns of use of drug therapy prior to PCI among patients with sCHD in Germany while taking patient characteristics and characteristics of regional healthcare supply into account. We found substantial variation in the prescription of guideline-recommended drug therapies for this patient group in routine practice and that the conservative therapy options are not fully exhausted prior to PCI. Although our study was not designed to determine whether poor guideline implementation is the cause of this variation, our findings can be used to formulate hypotheses to be used in further research on this topic and that there might be room for improvement in the care of patients with sCHD in Germany.

Author affiliations

[1]Department of Health Services Management, Munich School of Management, Ludwig-Maximilians-University Munich, Munich, Germany
[2]Institute for Medical Information Processing, Biometry, and Epidemiology, Ludwig-Maximilians-University Munich, Munich, Germany
[3]Pettenkofer School of Public Health, Munich, Germany
[4]AOK Bundesverband, Berlin, Germany
[5]Techniker Krankenkasse, Hamburg, Germany
[6]BARMER, Wuppertal, Germany
[7]Stiftung Institut für Herzinfarktforschung, Ludwigshafen, Germany
[8]Department of General Practice/Family Medicine, Philipps-University Marburg, Marburg, Germany
[9]Chair of Health Economics, Technical University Munich, Munich, Germany

Acknowledgements We thank Sebastian Franke for providing access to the data through the trust center.

Contributors JF-T led the development of the study design and methodology, conducted the data analysis and wrote the initial a draft of the manuscript. LS, ND-B, UZ, JB, DH-S and UM contributed to the conception of the work, critically reviewed and revised the draft for important intellectual content and contributed to the interpretation of the results.

Funding This study (01VSF16048) was funded by the innovation fund of the Federal Joint Committee (G-BA).

Competing interests JB is employed by the AOK Bundesverband, UM by the BARMER, DH-S by the TK. UZ reports personal fees from Astra Zeneca, Bayer, BMS, Daiichi Sankyo, Novartis, Sanofi, Amgen, Trommsdorf, Medicines Company, outside the submitted work. JF-T, ND-B and LS have nothing to declare.

Patient consent for publication Not required.

Ethics approval This study exclusively used anonymised billing data was therefore deemed exempt from ethics review and informed consent.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. The routine data analysed in this study are available from the statutory health insurances TK, AOK and BARMER, but restrictions apply to the availability of the data, which were used under licence for the current study and are not publicly available. To fulfil the legal requirements to obtain the data, researchers must obtain permission for a specific research question from the German Federal (Social) Insurance Office. Additionally, researchers must conclude a contract with the statutory health insurer regarding data access. The study must also be approved by the data protection officer both at the statutory health insurer and the research institute as well as the local ethics committee.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

ORCID iD

Julia Frank-Tewaag http://orcid.org/0000-0001-7881-1338

REFERENCES

1 Katritsis DG, Ioannidis JPA. Percutaneous coronary intervention versus conservative therapy in nonacute coronary artery disease: a meta-analysis. *Circulation* 2005;111:2906–12.
2 Bangalore S, Maron DJ, Stone GW, *et al*. Routine revascularization versus initial medical therapy for stable ischemic heart disease: a systematic review and meta-analysis of randomized trials. *Circulation* 2020;142:841–57.
3 Boden WE, O'Rourke RA, Teo KK, *et al*. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med* 2007;356:1503–16.
4 Hochman J, ed. *International study of comparative health effectiveness with medical and invasive approaches (ISCHEMIA): primary report of clinical outcomes. American Heart Association*

Annual Scientific Sessions (AHA 2019). Philadelphia, PA: American Heart Association, 2019.
5 Maron DJ, Hochman JS, Reynolds HR, *et al*. Initial invasive or conservative strategy for stable coronary disease. *N Engl J Med* 2020;382:1395–407.
6 BÄK, KBV, AWMF. *Nationale VersorgungsLeitlinie Chronische KHK – Langfassung*, 2014.
7 BÄK, KBV, AWMF. *Nationale VersorgungsLeitlinie Chronische KHK – Langfassung*, 2016.
8 Task Force M, Montalescot G, Sechtem U, *et al*. 2013 ESC guidelines on the management of stable coronary artery disease. *Eur Heart J* 2013;34:2949–3003.
9 Borden WB, Redberg RF, Mushlin AI, *et al*. Patterns and intensity of medical therapy in patients undergoing percutaneous coronary intervention. *JAMA* 2011;305:1882–9.
10 Garg P, Wijeysundera HC, Yun L, *et al*. Practice patterns and trends in the use of medical therapy in patients undergoing percutaneous coronary intervention in Ontario. *J Am Heart Assoc* 2014;3 doi:10.1161/JAHA.114.000882
11 Gorenoi V, Schönermark MP, Hagen A. Percutaneous coronary intervention with optimal medical therapy vs. optimal medical therapy alone for patients with stable angina pectoris. *GMS Health Technol Assess* 2011;7:Doc07.
12 Mangiapane S, Busse R. Prescription prevalence and continuing medication use for secondary prevention after myocardial infarction: the reality of care revealed by claims data analysis. *Dtsch Arztebl Int* 2011;108:856–62.
13 Reiner Ž, De Backer G, Fras Z, *et al*. Lipid lowering drug therapy in patients with coronary heart disease from 24 European countries--Findings from the EUROASPIRE IV survey. *Atherosclerosis* 2016;246:243–50.
14 Salzwedel A, Völler H, Reibis R, *et al*. [Regional aspects in treatment of patients with acute myocardial infarction in the North-East of Germany]. *Dtsch Med Wochenschr* 2018;143:e51–8.
15 Snaterse M, Khatibi S, Scholte Op Reimer WJM, *et al*. [Secondary prevention of coronary heart disease: results of Euroaspire IV]. *Ned Tijdschr Geneeskd* 2017;161:D643.
16 Zeymer U, Teilnehmer AR, ATKA-Register-Teilnehmer. [Secondary prevention in outpatients with coronary artery disease. Adherence with recommendations within 4 weeks after hospital discharge]. *Dtsch Med Wochenschr* 2007;132:2367–70.
17 De Backer G, Jankowski P, Kotseva K, *et al*. Management of dyslipidaemia in patients with coronary heart disease: results from the ESC-EORP EUROASPIRE V survey in 27 countries. *Atherosclerosis* 2019;285:135–46.
18 Aikens JE, Piette JD. Diabetic patients' medication underuse, illness outcomes, and beliefs about antihyperglycemic and antihypertensive treatments. *Diabetes Care* 2009;32:19–24.
19 Chan DC, Shrank WH, Cutler D, *et al*. Patient, physician, and payment predictors of statin adherence. *Med Care* 2010;48:196–202.
20 Chapman RH, Benner JS, Petrilla AA, *et al*. Predictors of adherence with antihypertensive and lipid-lowering therapy. *Arch Intern Med* 2005;165:1147–52.
21 Desai NR, Choudhry NK. Impediments to adherence to post myocardial infarction medications. *Curr Cardiol Rep* 2013;15:322.
22 DiMatteo MR. Variations in patients' adherence to medical recommendations: a quantitative review of 50 years of research. *Med Care* 2004;42:200–9.
23 Fischer MA, Choudhry NK, Brill G, *et al*. Trouble getting started: predictors of primary medication nonadherence. *Am J Med* 2011;124:1081.e9–22.
24 Hirsh BJ, Smilowitz NR, Rosenson RS, *et al*. Utilization of and adherence to Guideline-Recommended lipid-lowering therapy after acute coronary syndrome: opportunities for improvement. *J Am Coll Cardiol* 2015;66:184–92.
25 Jiang W, Glassman A, Krishnan R, *et al*. Depression and ischemic heart disease: what have we learned so far and what must we do in the future? *Am Heart J* 2005;150:54–78.
26 Kulik A, Shrank WH, Levin R, *et al*. Adherence to statin therapy in elderly patients after hospitalization for coronary revascularization. *Am J Cardiol* 2011;107:1409–14.
27 Baumhäkel M, Müller U, Böhm M. Influence of gender of physicians and patients on guideline-recommended treatment of chronic heart failure in a cross-sectional study. *Eur J Heart Fail* 2009;11:299–303.
28 Arnold SV, Kosiborod M, Tang F, *et al*. Patterns of statin initiation, intensification, and maximization among patients hospitalized with an acute myocardial infarction. *Circulation* 2014;129:1303–9.
29 Zullig LL, Stechuchak KM, Goldstein KM, *et al*. Patient-reported medication adherence barriers among patients with cardiovascular risk factors. *J Manag Care Spec Pharm* 2015;21:479–85.
30 Zullig LL, Shaw RJ, Shah BR, *et al*. Patient-provider communication, self-reported medication adherence, and race in a postmyocardial infarction population. *Patient Prefer Adherence* 2015;9:311–8.
31 Wissenschaftlichen Instituts der AOK (WIdO). *GKV-Arzneimittelindex des WIdO*, 2017.
32 Indikatoren und Karten zur Raum- und Stadtentwicklung [online], 2015. Available: https://www.inkar.de/
33 Kassenärztliche Bundesvereinigung (KBV). *Gesundheitsdaten - Medizinische Versorgung*, 2015.
34 Knopf H. [Drug usage of men and women with coronary heart disease. Results of the German Federal Health Survey 1998]. *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz* 2004;47:1051–5.
35 Riens BB-F J. *Leitliniengerechte therapie bei Herzinsuffizienz Zentralinstitut für die kassenärztliche Versorgung in Der Bundesrepublik Deutschland (Zi)*, 2014.
36 Reiner Z, Sonicki Z, Tedeschi-Reiner E. Physicians' perception, knowledge and awareness of cardiovascular risk factors and adherence to prevention guidelines: the PERCRO-DOC survey. *Atherosclerosis* 2010;213:598–603.
37 Drösler S. *Regionale Unterschiede in Der Operationshäufigkeit - Bewertung Der Daten und Handlungsbedarf*. Krefeld, Germany, 2015.
38 Möckel M, Searle J, Indikation JE. *Prognose und regionale Unterschiede Der Herzkatheterversorgung in Deutschland*. Wissenschaftlichen Instituts Der AOK (WIdO), 2014.
39 OECD. *Geographic variations in health care*, 2014.
40 Zhao M, Cooney MT, Klipstein-Grobusch K, *et al*. Simplifying the audit of risk factor recording and control: a report from an international study in 11 countries. *Eur J Prev Cardiol* 2016;23:1202–10.
41 Maron DJ, Boden WE, O'Rourke RA, *et al*. Intensive multifactorial intervention for stable coronary artery disease: optimal medical therapy in the courage (clinical outcomes utilizing revascularization and aggressive drug evaluation) trial. *J Am Coll Cardiol* 2010;55:1348–58.
42 Newman JD, Alexander KP, Gu X, *et al*. Baseline predictors of low-density lipoprotein cholesterol and systolic blood pressure goal attainment after 1 year in the ischemia trial. *Circ Cardiovasc Qual Outcomes* 2019;12:e006002.
43 Neubauer SZ, Lange J.;, A.; von der Schulenburg M. *Grundlagen und Methoden von GKV-Routinedatenstudie*. Hannover: Leibniz Universität, Center for Health Economics Research Hannover (CHERH), 2014.
44 Horenkamp-Sonntag D, Brüggenjürgen B, Stasun U, *et al*. Validität von Arzneimitteldaten in GKV-Routinedaten. *Monitor Versorgungsforschung* 2017;17.

We included combination therapies in our analysis if they contained any of the active substances recommended in the guidelines. For drugs with various indications, we considered only the ATC codes that were related to cardiovascular indications (see Table 1).

Table 1: Operationalization of drug therapy

Description	*ATC code*
Lipid-lowering agents	
Statins	C10AA, C10BA, C10BX
Other lipid-lowering therapies	C10AB, C10AC, C10AD, C10AX
Inhibitors of platelet aggregation	
ASA	B01AC06, C10BX01, C10BX02, C10BX04, C10BX05, C10BX06, C10BX08, C07FX04, C07FX02, C07FX03, C07FX04, B01AC56
Clopidogrel	B01AC04
Agents acting on the renin-angiotensin system	
ACE inhibitors	C09A, C09B, C10BX04, C10BX06, C10BX07, C10BX11
Angiotensin II receptor blockers (ARB)	C09C, C09D, C10BX10
Symptom-oriented therapy	
Beta-blockers	C07, C09BX02
Calcium channel blockers	C08, C07FB, C09DB, C10BX03, C10BX07, C10BX09, C10BX11, C07FB02, C07FB03, C07FB07, C07FB12, C07FB13 C09BX01, C09BB, C09DB
Ivabradine	C01EB17, C07FX05, C07FX06
Ranolazine	C01EB18
Organic nitrate	C01DA
Molsidomine	C01DX12

Both factors for which there is evidence of an association with poor use of guideline-recommended drug therapies or high rates of treatment discontinuation were considered in our analysis. The German and European guidelines recommend different measures to improve adherence, such as regularly addressing the topic in consultations with patients or the use of aids such as weekly blister packs (1-4). At the patient level, we included the following variables in our analysis: age, sex, participation in a disease management program (DMP), a history of cardiovascular events, a history of PCI or CABG, selected comorbidities, and the use of ambulatory services.

An analysis of the German Federal Health Survey in 1998 showed differences between men and women in the use of individual drugs for the treatment of CHD, suggesting, in turn, differences in the prescription behaviour of physicians in office-based practice according to the gender of their patients (5). In addition, the gender of patients is one of the most commonly observed predictors of non-compliance with drug therapy in patients with CHD. For example, whereas female gender has been shown to be a predictor of non-compliance with statin therapy (6), there is evidence that men are more likely to initiate and maximise such treatment (7). Similarly, women taking concomitant antihypertensive and lipid-lowering therapy are 10% less likely than men to adhere to it (8). A study in patients with heart failure in Germany has shown that among women in younger age groups, the use of guideline-recommended drug therapy is lower but approaches the level of use in men with increasing age (9). Lastly, the results of a cross-sectional study in Germany suggest that the gender of the treating physician and the patient may influence the likelihood of whether guideline recommendations for the treatment of chronic heart failure are followed (10).

A patient’s history and prior treatment of CHD may also have an impact on adherence. It has been shown that an index prescription of statins following an acute coronary syndrome is associated with higher rates of compliance (6). Moreover, patients with a higher risk of CHD had a higher adherence to antihypertensive and lipid-lowering therapy than did patients without CHD risk factors. For example, in patients with an acute or previous myocardial infarction in the year preceding drug treatment initiation, the odds of adherence was 28% greater than that among patients without evidence of CHD (8). In addition, a correlation has been found between certain comorbidities and the use of and compliance with drug therapy, including hypertension, heart failure, diabetes mellitus, disorders of lipid metabolism, peripheral arterial disease (PAD), depression and dementia (6-8, 11-17). We determined patients’ cardiac history and comorbidities from the ICD-10-encoded diagnoses in the quarters prior to the index PCI according to the M2Q criteria (i.e., an inpatient primary or secondary diagnosis or confirmed office-based diagnosis in at least two quarters). The included ICD-10 codes and procedures are listed in Table 1.

Table 1: Operationalization of diagnoses and procedures

Description	*ICD-10 codes*
Prior myocardial infarction	I21 - I24, I25.2
Hypertension	I10 - I13, I15
Disorders of lipid metabolism	E78
Heart failure	I50
Diabetes mellitus (type I & II)	E10 - E14
Depression	F31 - F33
Dementia	F00 - F03, F05.1, G30 - G31
Description	*Procedure codes*
PCI	EBM: 34292, OPS: 8-837
CABG	OPS: 5-361, 5-362

Patients' use of medical services can also influence prescription prevalence. The results of an analysis of routine data from a statutory health insurer in Germany (18, 19) suggest that a combination of primary and specialist care is associated with the highest prevalence of prescriptions for guideline-recommended therapies in most drug groups in the treatment of heart failure. An analysis of data from the Association of Statutory Health Insurance Physicians yielded a similar finding (9). We classified patients' use of office-based physician services based on their visits to GPs, primary care internists and cardiologists because these are the groups of physicians who are usually involved in the office-based care of patients with CHD in Germany. We considered patients with fewer than two visits per year to be low users of office-based physician services. We classified the remaining patients according to whether they had made (1) two or more visits to a GP or primary care internist and (2) an additional visit to the cardiologist.

In addition to patient-specific factors, regional factors may play a role in the use of recommended drug therapies. At the level of the regional supply of health services, these include access to care and the average number of cases per physician. Although service density in Germany is generally high, there are regional differences in the accessibility of care. On the one hand, high workloads for providers can lead to shorter physician-patient interactions, potentially reducing the capacity and time that providers have to discuss and review treatment. This, in turn, could lead to a reduction in prescription prevalence or adherence. On the other hand, a high volume of cases might enhance providers' experience and skills, possibly increasing their propensity to prescribe the recommended drug therapy. In a study of patients with heart failure in Germany in 2014, regional differences characterised by an east-west gradient were observed in the prescription of guideline-recommended drug therapy. The highest proportion of patients with the appropriate drug therapy was found in Mecklenburg-Western Pomerania, Brandenburg, Saxony, and Saxony-Anhalt in eastern Germany. There was also evidence that co-supervision by a cardiologist minimised this east-west difference even though an east-west gradient in cardiologist density could not be demonstrated with the available data (9).

In order to examine how physician density and patients' use of office-based physician services might impact the use of guideline-recommended drug therapy for CHD, we considered features of the regional health care supply at the district level. For this purpose, we assigned patients to the 401 administrative districts in Germany based on the last available information about their place of residence. At the district level, we approximated access to care based on the density of pharmacies (per 100,000 inhabitants, 2015) (20), general practitioners (per 100,000 inhabitants, 2015) (21) and internists (per 100,000 inhabitants, 2015) (20). Furthermore, we approximated patients' use of regional health care services based on the average number of cases per family doctor (21) and the average number of cases per internist (20, 21). In addition, we considered whether the districts were in eastern or western Germany, the former of which we defined as comprising the five new states that were formed after German Reunification in 1990.

References

1. Bundesärztekammer (BÄK) KBK, Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF). Nationale VersorgungsLeitlinie Chronische KHK. 2014;3. Auflage(Version 1).
2. Bundesärztekammer (BÄK) KBK, Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF). Nationale VersorgungsLeitlinie Chronische KHK 2016; 4. Auflage.
3. Bundesärztekammer (BÄK) KBK, Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF). Nationale VersorgungsLeitlinie Chronische KHK – Langfassung. 2019; 5. Auflage(Version 1).
4. Task Force M, Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, et al. 2013 ESC guidelines on the management of stable coronary artery disease. Eur Heart J. 2013;34(38):2949-3003.
5. Knopf H. [Drug usage of men and women with coronary heart disease. Results of the German Federal Health Survey 1998]. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz. 2004;47(11):1051-5.
6. Chan DC, Shrank WH, Cutler D, Jan S, Fischer MA, Liu J, et al. Patient, physician, and payment predictors of statin adherence. Med Care. 2010;48(3):196-202.
7. Arnold SV, Kosiborod M, Tang F, Zhao Z, Maddox TM, McCollam PL, et al. Patterns of statin initiation, intensification, and maximization among patients hospitalized with an acute myocardial infarction. Circulation. 2014;129(12):1303-9.
8. Chapman RH, Benner JS, Petrilla AA, Tierce JC, Collins SR, Battleman DS, et al. Predictors of adherence with antihypertensive and lipid-lowering therapy. Arch Intern Med. 2005;165(10):1147-52.
9. Riens BB-F, J.;. Leitliniengerechte Therapie bei Herzinsuffizienz Zentralinstitut für die kassenärztliche Versorgung in der Bundesrepublik Deutschland (Zi); 2014.
10. Baumhakel M, Muller U, Bohm M. Influence of gender of physicians and patients on guideline-recommended treatment of chronic heart failure in a cross-sectional study. Eur J Heart Fail. 2009;11(3):299-303.
11. Zeymer U, Teilnehmer AR. [Secondary prevention in outpatients with coronary artery disease. Adherence with recommendations within 4 weeks after hospital discharge]. Dtsch Med Wochenschr. 2007;132(45):2367-70.
12. Kulik A, Shrank WH, Levin R, Choudhry NK. Adherence to statin therapy in elderly patients after hospitalization for coronary revascularization. Am J Cardiol. 2011;107(10):1409-14.
13. Hirsh BJ, Smilowitz NR, Rosenson RS, Fuster V, Sperling LS. Utilization of and Adherence to Guideline-Recommended Lipid-Lowering Therapy After Acute Coronary Syndrome: Opportunities for Improvement. J Am Coll Cardiol. 2015;66(2):184-92.
14. Garg P, Wijeysundera HC, Yun L, Cantor WJ, Ko DT. Practice patterns and trends in the use of medical therapy in patients undergoing percutaneous coronary intervention in Ontario. J Am Heart Assoc. 2014;3(4).
15. Fischer MA, Choudhry NK, Brill G, Avorn J, Schneeweiss S, Hutchins D, et al. Trouble getting started: predictors of primary medication nonadherence. Am J Med. 2011;124(11):1081 e9-22.
16. Aikens JE, Piette JD. Diabetic patients' medication underuse, illness outcomes, and beliefs about antihyperglycemic and antihypertensive treatments. Diabetes Care. 2009;32(1):19-24.
17. Jiang W, Glassman A, Krishnan R, O'Connor CM, Califf RM. Depression and ischemic heart disease: what have we learned so far and what must we do in the future? Am Heart J. 2005;150(1):54-78.

18. Neubauer S, Zeidler J, Schilling T, Engel S, Linder R, Verheyen F, et al. Suitability and Usability of Claims Data for Review of Guidelines for the Treatment of Chronic Heart Failure. Gesundheitswesen. 2016;78(S 01):e135-e44.
19. Neubauer S, Schilling T, Zeidler J, Lange A, Engel S, Linder R, et al. [Impact of guideline adherence on mortality in treatment of left heart failure]. Herz. 2016;41(7):614-24.
20. Bundesinstitut für Bau- S-uRBB. Indikatoren und Karten zur Raum- und Stadtentwicklung. 2018.
21. Kassenärztliche Bundesvereinigung (KBV). Gesundheitsdaten - Medizinische Versorgung. 2015.

References

1. Frank-Tewaag J, Bleek J, Günster C, Schneider U, Horenkamp-Sonntag D, Marschall U, et al. Regional variation in coronary angiography rates: the association with supply factors and the role of indication: a spatial analysis. BMC Cardiovascular Disorders. 2022;22(1):72.

2. Frank-Tewaag J, Bleek J, Horenkamp-Sonntag D, Marschall U, Zeymer U, Donner-Banzhoff N, et al. Use of guideline-recommended drug therapy in patients undergoing percutaneous coronary intervention for stable coronary heart disease in Germany: a multilevel analysis of nationwide routine data. BMJ Open. 2020;10(12):e042886.

3. Leitliniengrundlagen. Versorgungsleitlinien [Internet]. 2016 September 12. Available from: http://www.leitlinien.de/leitlinien-grundlagen.

4. Wennberg JE, Fisher ES, Skinner JS. Geography and the debate over Medicare reform. Health Aff (Millwood). 2002;Suppl Web Exclusives:W96-114.

5. Chandra A, Skinner J. Technology Growth and Expenditure Growth in Health Care. Journal of Economic Literature. 2012;50(3):645-80.

6. Destatis. Häufigsten Todesursachen 2016. 2019.

7. Todesursachenstatistik ab 1998, Sterbefälle, Sterbeziffern (je 100.000 Einwohner, altersstandardisiert). [Internet]. 2014. Available from: www.gbe-bund.de.

8. Destatis. Fallpauschalenbezogene Krankenhausstatistik (DRG-Statistik) Operationen und Prozeduren der vollstationären Patientinnen und Patienten in Krankenhäusern 2019

9. Dissmann W, de Ridder M. The soft science of German cardiology. Lancet. 2002;359(9322):2027-9.

10. Möckel M, Searle J, Jeschke E. Indikation, Prognose und regionale Unterschiede der Herzkatheterversorgung in Deutschland (Hrsg.): Schattauer-Verlag: Stuttgart; 2014. In: Klauber J GC, Gerste B, Robra B-P, Schmacke N, editor. Versorgungs-Report 2013/2014. Stuttgart: Schattauer-Verlag; 2014.

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

12. Storz-Pfennig. Germany: Geographic variations in health care. Geographic Variations in Health Care: What do we know and what can be done to improve health system performance? Paris: OECD Publishing; 2014. p. 254 - 60.

13. Bundesärztekammer (BÄK) KBK, Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF). Nationale VersorgungsLeitlinie Chronische KHK – Langfassung. 2019; 5. Auflage(Version 1).

14. Bundesärztekammer (BÄK) KBK, Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF). Nationale VersorgungsLeitlinie Chronische KHK – Langfassung. 2014;3. Auflage(Version 1).

15. Bundesärztekammer (BÄK) KBK, Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF). Nationale VersorgungsLeitlinie Chronische KHK – Langfassung. 2016; 4. Auflage(Konsultationsfassung).

16. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J. 2020;41(3):407-77.

17. Task Force M, Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the

Task Force on the management of stable coronary artery disease of the European Society of Cardiology. Eur Heart J. 2013;34(38):2949-3003.

18. Neubauer SZ, J.; Lange, A.; von der Schulenburg, M. Grundlagen und Methoden von GKV-Routinedatenstudie. Hannover: Leibniz Universität, Center for Health Economics Research Hannover (CHERH); 2014.

19. Swart E, Graf von Stillfried D, Koch-Gromus U. Kleinräumige Versorgungsforschung. Bundesgesundheitsblatt - Gesundheitsforschung - Gesundheitsschutz. 2014;57(2):161-3.

20. Swart E. Über-, Unter- und Fehlversorgung in der stationären Versorgung –

Welche Rückschlüsse lassen sich aus GKV-Routinedaten ziehen? . In: Swart E, Ihle P, editors. Routinedaten im Gesundheitswesen – Handbuch Sekundärdatenanalyse: Grundlagen, Methoden und Perspektiven 1. Bern: Verlag Hans Huber; 2005. p. 253–62.

21. Novelli A, Frank-Tewaag J, Bleek J, Gunster C, Schneider U, Marschall U, et al. Identifying and Investigating Ambulatory Care Sequences Before Invasive Coronary Angiography. Med Care. 2022;60(8):602-9.

22. Hartwell D, Colquitt J, Loveman E, Clegg AJ, Brodin H, Waugh N, et al. Clinical effectiveness and cost-effectiveness of immediate angioplasty for acute myocardial infarction: systematic review and economic evaluation. Health Technol Assess. 2005;9(17):1-99, iii-iv.

23. Jung C, Elsasser A. [Update ESC Guideline 2017 - Acute Myocardial Infarction (STEMI)]. Dtsch Med Wochenschr. 2018;143(11):797-801.

24. Gorenoi V, Schonermark MP, Hagen A. Percutaneous coronary intervention with optimal medical therapy vs. optimal medical therapy alone for patients with stable angina pectoris. GMS Health Technol Assess. 2011;7:Doc07.

25. Stone GW, Hochman JS, Williams DO, Boden WE, Ferguson TB, Jr., Harrington RA, et al. Medical Therapy With Versus Without Revascularization in Stable Patients With Moderate and Severe Ischemia: The Case for Community Equipoise. J Am Coll Cardiol. 2016;67(1):81-99.

26. Kroll LE, Schumann M, Hoebel J, Lampert T. Regional health differences – developing a socioeconomic deprivation index for Germany. Robert Koch-Institut, Epidemiologie und Gesundheitsberichterstattung %J Journal of Health Monitoring; 2017.

27. Referenzdatenbank: Die Qualitätsberichte der Krankenhäuser [Internet]. 2017 [cited 2019]. Available from: https://g-ba-qualitaetsberichte.de/#search.

28. Ibanez B, Librero J, Bernal-Delgado E, Peiro S, Lopez-Valcarcel BG, Martinez N, et al. Is there much variation in variation? Revisiting statistics of small area variation in health services research. BMC Health Serv Res. 2009;9:60.

29. Kelejian HH, Prucha IR. A Generalized Moments Estimator for the Autoregressive Parameter in a Spatial Model. International Economic Review. 2001;40(2):509-33.

30. Boden WE, O'Rourke RA, Teo KK, Hartigan PM, Maron DJ, Kostuk WJ, et al. Optimal medical therapy with or without PCI for stable coronary disease. N Engl J Med. 2007;356(15):1503-16.

31. Hochman J, editor International Study Of Comparative Health Effectiveness With Medical And Invasive Approaches (ISCHEMIA): Primary Report of Clinical Outcomes. American Heart Association Annual Scientific Sessions (AHA 2019); 2019; Philadelphia, PA, US: AHA.

32. Katritsis DG, Ioannidis JP. Percutaneous coronary intervention versus conservative therapy in nonacute coronary artery disease: a meta-analysis. Circulation. 2005;111(22):2906-12.

33. Bundesinstitut für Bau- S-uRBB. Indikatoren und Karten zur Raum- und Stadtentwicklung. 2018.

34. Kassenärztliche Bundesvereinigung (KBV). Gesundheitsdaten - Medizinische Versorgung. 2015.

35. Blumel M, Spranger A, Achstetter K, Maresso A, Busse R. Germany: Health System Review. Health Syst Transit. 2020;22(6):1-272.

36. Horenkamp-Sonntag D, Brüggenjürgen B, Stasun U, Berghöfer A, Willich S. Validität von Arzneimitteldaten in GKV-Routinedaten. Monitor Versorgungsforschung. 2017;17(03).

37. Shrier I, Platt RW. Reducing bias through directed acyclic graphs. BMC Med Res Methodol. 2008;8:70.

38. Jürges H. Health Insurance Status and Physician Behavior in Germany. Schmollers Jahrbuch : Journal of Applied Social Science Studies / Zeitschrift für Wirtschafts- und Sozialwissenschaften. 2009;129(2):297-307.

39. Kopetsch T, Schmitz H. Regional variation in the utilisation of ambulatory services in Germany. Health Econ. 2014;23(12):1481-92.

Acknowledgements

First and foremost, I want to thank my supervisor Leonie Sundmacher for her continuous support, advice, and mentorship throughout the PhD project. Also, I would like to thank Eva Grill and Ulrich Mansmann for their advice and feedback as part of the thesis advisory committee. A special thank you goes to my fellow students Anna Novelli and Isabel Geiger for being great sparing partners and for always having an open ear. Lastly, I would like to thank my husband and the entire family for their continuous support, and I am grateful for my twin boys, who made this time even more adventurous.

List of all scientific publications

Wagner A. Tewaag J. Sahakyan N. Scheuringer M. Krobot K. J. (2014) Unbedingte exakte Tests: Eine SAS-basierte Lösung zur effizienten Berechnung für Stichprobengrößen Uber 1000; published in: KFSE SAS Wiki

Sundmacher, L., Schang, L., Schüttig, W., Flemming, R., Frank-Tewaag, J., Geiger, I., Franke, S., Weinhold, I., Wende, D., Kistemann, T., Höser, C., Kemen, J., Hoffmann, W., van den Berg, N., Kleinke, F., Becker, U., Brechtel, T. (2018). Gutachten zur Weiterentwicklung der Bedarfsplanung i.S.d. §§ 99 ff. SGB V zur Sicherung der vertragsärztlichen Versorgung. On behalf of Gemeinsamen Bundesausschusses

Frank-Tewaag, J., Bleek, J., Horenkamp-Sonntag, D., Marschall, U., Zeymer, U., Donner-Banzhoff, N., & Sundmacher, L. (2020). Use of guideline-recommended drug therapy in patients undergoing percutaneous coronary intervention for stable coronary heart disease in Germany: a multilevel analysis of nationwide routine data. BMJ Open, 10(12), e042886. doi: 10.1136/bmjopen-2020-042886.

Frank-Tewaag, J., Bleek, J., Günster, C., Schneider, U., Horenkamp-Sonntag, D., Marschall, U., Franke, S., Schlößler, K., Donner-Banzhoff, N., & Sundmacher, L. (2022). Regional variation in coronary angiography rates: the association with supply factors and the role of indication: a spatial analysis. BMC Cardiovascular Disorders, 22(1), 72. doi: 10.1186/s12872-022-02513-z.

Novelli, A., Frank-Tewaag, J., Bleek, J., Günster, C., Schneider, U., Marschall, U., Schlößler, K., Donner-Banzhoff, N., & Sundmacher, L. (2022). Identifying and Investigating Ambulatory Care Sequences Before Invasive Coronary Angiography. Medical Care, 60(8), 602-609. doi: 10.1097/MLR.0000000000001738.