

**Opportunities and challenges of heart failure prevention:
cost-effective screening and guideline-adherent care
in risk populations**

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Summary

Heart Failure (HF) is a chronic disease with a significant clinical and economic burden for patients and healthcare systems worldwide. Due to an expected increase in the prevalence of HF, resulting from the demographic change and the improved survival of those affected, HF prevention gains increasing importance. While focusing on a novel screening program for preventing or delaying the onset of HF, this dissertation explored challenges and opportunities associated with different determinants of HF prevention in three dissertation projects (DPs).

Since the early identification and management of patients with pre-HF (presymptomatic structural cardiac damage) is crucial for HF prevention, DPs I and II evaluated a structured pre-HF screening program based on the global longitudinal strain (GLS), an innovative systolic function parameter. DP I assessed the prevalence of pre-HF (defined as $GLS \geq -15\%$) in a German at-risk population in a cross-sectional study and estimated the time gained before the diagnosis of (symptomatic) HF compared with an entropy balanced historical control group. DP II investigated the cost-effectiveness of the GLS-based pre-HF screening program using a decision-analytic model.

For individuals with an increased risk of HF, evidence-based care as recommended in clinical practice guidelines (CPGs) is needed to prevent or delay the onset of (symptomatic) HF. To provide detailed information for targeted interventions, DP III therefore used regression analyses to evaluate differences in healthcare providers' guideline adherence for coronary angiographies (CAs) in women and men with suspected coronary artery disease (CAD; the most common reason of HF) as an example.

The GLS-based screening revealed a 23% pre-HF prevalence and enabled a pre-HF diagnosis about 7 years before a (symptomatic) HF diagnosis in standard of care (SoC). In the long term, the model showed an improved life expectancy and considerable additional costs for the GLS-based screening program compared with SoC. Significant sex differences were observed in the guideline adherence in the diagnostic work-up of CAD, with CAs being less likely guideline-adherent in women than men.

The results of this dissertation emphasize the importance of increasing awareness of pre-HF and establishing a structured screening program. A GLS-based pre-HF screening program seems to be a promising approach. However, further research is required to increase the robustness of the results and to improve cost-effectiveness. Furthermore, the results support the consideration of sex differences in guideline-adherence in the development of targeted intervention to improve evidence-based care in patients at risk of HF.

Zusammenfassung

Herzinsuffizienz (HI) ist eine chronische Erkrankung mit einer weltweit hohen klinischen und ökonomischen Belastung für Patient*innen und Gesundheitssysteme. Aufgrund einer erwarteten Steigerung der Prävalenz der HI durch den demographischen Wandel und verbesserte Überlebensraten Betroffener gewinnt die Prävention der HI zunehmend an Bedeutung. Mit Fokus auf ein neuartiges Screening-Programm zur Verhinderung oder Verzögerung der Entwicklung einer HI untersuchte diese Dissertation in drei Dissertationsprojekten (DPs) Chancen und Herausforderungen verschiedener Determinanten der HI-Prävention.

Da vor allem die frühzeitige Identifikation und Versorgung von prä-HI (präsymptomatische strukturelle Herzschäden) entscheidend für die HI-Prävention sind, evaluierten DP I und II ein strukturiertes prä-HI Screening-Programm basierend auf dem globalen longitudinalen Strain (GLS), einem innovativen systolischen Funktionsparameter. DP I untersuchte dabei die Prävalenz der prä-HI (definiert als $GLS \geq -15\%$) in einer deutschen Risikopopulation mittels einer Querschnittstudie und schätzte die gewonnene Zeit vor der Diagnose einer (symptomatischen) HI gegenüber einer gewichteten historischen Kontrollgruppe. DP II evaluierte die Kosten-Effektivität des Programms unter Verwendung eines entscheidungsanalytischen Modells.

Bei Personen mit erhöhtem HI-Risiko ist zur Verzögerung oder Verhinderung des Auftretens einer (symptomatischen) HI eine evidenz-basierte, in klinischen Leitlinien empfohlene, Versorgung notwendig. Zur Entwicklung gezielter Interventionen untersuchte DP III daher mittels Regressionsanalysen exemplarisch Unterschiede in der Leitlinienadhärenz der Leistungserbringenden in der Durchführung von Koronarangiographien in Frauen und Männern mit vermuteter koronarer Herzkrankheit (KHK; häufigste Ursache der HI).

Das GLS-basierte Screening zeigte eine prä-HI-Prävalenz von 23% und ermöglichte die Diagnose einer prä-HI etwa 7 Jahre vor der einer (symptomatischen) HI in der Regelversorgung. Langfristig zeigte das Modell für das Screening-Programm eine höhere Lebenserwartung sowie zusätzliche Kosten verglichen mit der Regelversorgung. In der Leitlinienadhärenz bei der Diagnose einer KHK ergaben sich signifikante Geschlechterunterschiede, mit weniger leitlinienadhärenten Koronarangiographien bei Frauen.

Die Ergebnisse dieser Dissertation verdeutlichen die Notwendigkeit, das Bewusstsein für prä-HI zu steigern und ein strukturiertes Screening-Programm zu etablieren. Der GLS-basierte Ansatz erscheint vielversprechend, weitere Forschung ist jedoch notwendig, um die Robustheit der Ergebnisse zu steigern und die Kosten-Effektivität zu erhöhen. Zudem bekräftigen die Ergebnisse die Berücksichtigung von Geschlechterunterschieden in der Leitlinienadhärenz bei der Entwicklung gezielter Maßnahmen zur Förderung einer evidenzbasierten Versorgung von Personen mit erhöhtem HI-Risiko.

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List of abbreviations

ACC	American College of Cardiology	HFpEF	Heart Failure with preserved Ejection Fraction
ACE	Angiotensin-Converting-Enzyme	HFrEF	Heart Failure with reduced Ejection Fraction
ACS	Acute Coronary Syndrome	ICD	International Classification of Diseases
AHA	American Heart Association	ICER	Incremental Cost-Effectiveness Ratio
AI-ECG	Artificial Intelligence Electrocardiogram	JACARDI	Joint Action on cardiovascular diseases and diabetes
AOK	Allgemeine Ortskrankenkasse [General local health insurance fund]	LVEF	Left Ventricular Ejection Fraction
ARB	Angiotensin II Receptor Blocker	LY	Life Year
BB	Beta Blocker	MI	Myocardial Infarction
BNP	B-type Natriuretic Peptide	NT-proBNP	N-terminal pro-B-type Natriuretic Peptide
CA	Coronary Angiography	NYHA	New York Heart Association
CAD	Coronary Artery Disease	OR	Odds Ratio
CCS	Chronic Coronary Syndrome	OV	Option Value
CMR	Cardiac Magnetic Resonance	pre-HF	pre-Heart Failure
CPG	Clinical Practice Guideline	QALY	Quality Adjusted Life Year
DP	Dissertation Project	RCT	Randomized Controlled Trial
ECHO	Echocardiography	SHI	Statutory Health Insurance
ESC	European Society of Cardiology	SoC	Standard of Care
GLS	Global Longitudinal Strain	STM	State-Transition Model
GNDMG	German National Disease Management Guideline	U.S.	United States
HF	Heart Failure	WTP	Willingness-To-Pay
HFmEF	Heart Failure with mildly reduced Ejection Fraction		

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Chapter 1

Introduction

1 Introduction

Heart failure (HF) is considered as global pandemic that is associated with a significant clinical and economic burden¹. Evidence suggest that HF affects about 1 to 3% of the adult population and is responsible for 1 to 2% of all hospital admissions worldwide¹. In addition, despite improvements in HF prognosis, mortality of HF patients remains high¹. In the last years, HF was estimated to account for around 3 to 9% of the global healthcare expenditure²⁻⁴.

In the future, the increasing prevalence of risk factors such as hypertension and the demographic change will lead to an increase in the number of people at high risk of HF. In addition, further advancements in HF management will improve the survival of affected patients. Thus, the prevalence and burden of HF is expected to rise further⁵⁻⁷. To address this increase, structured HF prevention plays a fundamental role^{5,8,9}.

The overall aim of this dissertation is to explore opportunities and challenges of HF prevention. While focusing on an innovative screening and prevention approach, different determinants of HF prevention are addressed by applying various methods of analysis: Firstly, to prevent or delay the onset of symptomatic HF, an early identification and management of individuals at risk is essential^{5,8}. Thus, the diagnostic potential of a structured pre-HF screening and prevention program (in the following, the term ‘screening program’ is used that refers to screening and prevention measures¹⁰) was evaluated using descriptive statistics and weighted comparison of means¹¹. Secondly, innovative screening approaches have to demonstrate their additive value compared with standard care¹². Thus, a model-based health economic evaluation of the long-term cost-effectiveness of a structured pre-HF screening program was performed¹³. Thirdly, to prevent or delay the onset of HF, people at risk of HF need to receive evidence-based care such as recommended in clinical practice guidelines (CPGs)¹⁴. To develop targeted interventions, regression analyses were used to examine patient-related sex differences in healthcare providers’ guideline adherence (i.e., extent to which they follow CPGs^{15,16}) in the diagnosis of the most common reason of HF (i.e., coronary artery disease (CAD)^{17,18}) as an example¹⁹.

Chapter 2 provides an overview of the rationale and the current evidence on the research topic. It outlines the theoretical background on medical aspects of HF including CAD as risk factor (2.1), the clinical and economic burden of HF (2.2), and the screening for and prevention of HF including affecting factors such as cost-effectiveness and guideline adherence (2.3). The overall aim of this cumulative dissertation and the objectives of each dissertation project (DP) are presented in chapter 3. Chapters 4 to 6 describe the methods, present the scientific publications,

and summarize the key findings of the DPs. In chapter 7, the results of this cumulative dissertation are compared with the current state of research, methodological strengths and limitations are described, and opportunities and challenges of HF prevention are derived. In addition, implications for research, policy, and clinical practice are presented. Finally, a conclusion is drawn in chapter 8.

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Chapter 2

Theoretical background

2 Theoretical background

2.1 Heart failure as a clinical syndrome

2.1.1 The definition and classification of heart failure

HF is a complex clinical syndrome with typical symptoms (e.g., breathlessness, fatigue, ankle swelling) and/or specific signs (e.g., elevated jugular venous pressure, third heart sound) confirmed by elevated natriuretic peptide levels or objective evidence of systemic or cardiogenic pulmonary congestion¹. It is caused by structural and/or functional cardiac abnormalities¹ resulting in the heart's incapacity to sufficiently supply the organism with blood and oxygen for a stable metabolism². HF may present as chronic HF, described as gradual onset of symptoms, or acute HF with sudden deterioration that requires an urgent evaluation^{2,3}.

The classification of HF has therapeutically and prognostic implications and can be based on different criteria. In clinical trials and clinical guideline recommendations, HF is often categorized according to the left ventricular ejection fraction (LVEF)¹⁻³, a left ventricular systolic function parameter measuring the proportion of blood pumped out of the heart during one contraction⁴. This classification distinguishes between HF with reduced ($\leq 40\%$) LVEF (HFrEF), mildly reduced ($>40\%$ to $<50\%$) LVEF (HFmEF), and preserved ($\geq 50\%$) LVEF (HFpEF)³.

In addition, HF is often classified according to symptom severity using the New York Heart Association (NYHA) states I (i.e., no limitation of physical activity) to IV (i.e., no physical activity without discomfort)^{3,5}. Based only on the patients' performance this is a subjective classification^{2,3,6}.

Furthermore, since 2001, the American College of Cardiology (ACC) and the American Heart Association (AHA) describe HF as continuum and classify four HF stages based on the disease progression⁷. The latest definition of the stages⁶ is presented in Table 1. Briefly, patients in stage A/at risk of HF are asymptomatic with typical risk factors but no structural heart disease; Patients in stage B/with pre-HF are still asymptomatic but have structural heart disease; Patients in stage C/with HF have current or previous symptoms and/or signs of HF; Patients in stage D/with advanced HF have severe symptoms and/or signs of HF that interfere with daily life functions^{1,6}.

Table 1: Heart failure stages (adapted from Heidenreich et al., 2022⁶)

Stage	Description	Definition
A	At risk for HF	– no current/previous symptoms and signs – AND presence of risk factors (e.g., diabetes mellitus, obesity, hypertension, atherosclerotic cardiovascular disease) – AND no structural/functional heart disease or abnormal biomarkers
B	Pre-HF	– no current/previous symptoms and signs AND – presence of risk factors (e.g., diabetes mellitus, obesity, hypertension, atherosclerotic cardiovascular disease) with increased natriuretic peptides or elevated cardiac troponin – OR structural heart disease (e.g., reduced ejection fraction, reduced strain, ventricular hypertrophy) – OR evidence for increased filling pressures (e.g., by noninvasive imaging)
C	Symptomatic HF	– Structural heart disease with current/previous symptoms or signs of HF
D	Advanced HF	– HF symptoms interfering with daily life and recurrent hospitalizations despite optimized guideline-directed medical therapy that require advance therapies (e.g., transplantation)

HF = Heart Failure

2.1.2 The pathophysiology, etiology, and risk factors of heart failure

The development of HF involves various pathophysiological mechanisms⁸. Briefly, it begins with an impaired left ventricular function (e.g., resulting from pressure and/or volume load or loss of tissue). This myocardial injury leads to a reduced cardiac output and initiates neurohormonal counter-regulatory mechanisms to maintain the heart function (e.g., activation of the sympathetic or renin-angiotensin-aldosterone system)^{2,9,10}. While these mechanisms may improve cardiac output in the short term, they lead to further myocardial damage and a manifestation of HF in the long-term^{2,11}.

Risk factors of HF can be manifold^{2,12,13}. In the western world, the most common and strongest risk factors of HF are CAD and hypertension^{2,3,12,14–16}, accounting for up to >50% of all HF cases^{2,15}. Other common risk factors are, for example, cardiomyopathies, valvular heart disease, arrhythmias, and diabetes^{2,17–19}. In addition, lifestyle factors such as physical inactivity, obesity, increased alcohol consumption, and smoking are strongly associated with an increased lifetime risk of HF^{2,6,20,21}. For example, severe overweight is associated with a doubled risk of HF, and smoking leads to an increase by around 50%²².

While evidence on sex differences in lifestyle factors' impact on HF is limited, considerable differences were observed in traditional risk factors^{23,24} such as hypertension (three-fold HF risk in women, two-fold risk in men) and diabetes mellitus (five-fold HF risk in women, two-fold risk in men)^{25,26}. In addition, some sex-specific risk factors elevate the risk in women, such as pregnancy-related factors (e.g., peripartum cardiomyopathy) or breast cancer therapy-related factors (e.g., radiation)^{23,24}.

2.1.3 Coronary artery disease as a cause of heart failure

CAD, also known as ischemic or coronary heart disease, is the clinical manifestation of atherosclerosis in the coronary arteries²⁷. The buildup of atherosclerotic plaque narrows the diameter of the coronary arteries that partly or completely blocks the blood flow. This may cause an inadequate blood and oxygen supply to the myocardium, which can result in myocardial ischemia^{28,29}.

With increasing obstruction of the arteries, patients are more likely to develop various symptoms^{27,30}. While the most common symptom is heart-related chest pain or discomfort (i.e., angina pectoris)^{27,30–32}, symptoms may be ambiguous, with less specific and 'atypical' ones particularly in women^{33,34}. In addition, patients can also remain asymptomatic^{27,30,32}, making a reliable diagnosis of CAD difficult³⁰.

CAD is a chronic and often progressive disease. Stable periods (i.e., chronic CAD or chronic coronary syndrome (CCS)) may be interrupted by unstable periods (i.e., acute coronary syndrome (ACS)), in most cases as a result of a thrombosis^{28,32}.

The inadequate supply of the myocardium can cause structural damage that might decrease myocardial function³⁵, a pathophysiological mechanism of HF^{9,10}. In particular, damage due to myocardial infarction (MI) as type of ACS, structural remodeling processes, and chronic circulatory disorders can lead to a progressive deterioration in heart function and contribute to HF^{13,35–37}.

2.2 The burden of heart failure

2.2.1 The epidemiology of heart failure and coronary artery disease

HF is a global health problem, presenting with an incidence of 3 per 1,000 patient years and more than 64 million people (1 to 3% of the adult population) affected in 2017^{18,38}. In Germany, an incidence of even 6.6 per 1,000 patient years was reported³⁹, and about 5.5% of the population was affected in 2024⁴⁰.

The HF incidence is estimated to remain stable or to decline. In contrast, the HF prevalence is expected to rise further due to an increase in the number of people at high risk of HF and an improved survival rate of HF patients resulting from an increasing overall life expectancy and advances in HF management (e.g., life-prolonging HF therapies, earlier diagnosis, and better management of comorbidities)^{18,41–44}. Data on the prevalence stratified by HF stages is limited, and estimates vary from 22 to 52% for stage A, from 24 to 43% for stage B, and from 2 to 13% for stage C/D⁴⁵.

With prevalence and incidence rates increasing with age, HF affects particularly the elderly^{20,46–51}. Sex-specific evidence is inconclusive, reporting either similar HF incidence and prevalence rates for both sexes or higher rates for men compared with women^{48–52}.

Accounting for 20 to >70% of HF cases^{14,15,19,35,53}, CAD is argued to be the most common cause of HF^{35,37}. Since a higher population attributable risk for HF associated with CAD was observed in men than women, the contribution of CAD to HF appears to be stronger in men^{13,35}. In addition, the combined occurrence of CAD and HF is associated with a worse prognosis than HF alone (i.e., higher risk of hospitalization, higher mortality)^{35,54}.

CAD affected 2% of the global population in 2017 and 8% of the German population in 2024, with a higher prevalence in men than in women (10% vs. 6% in Germany)^{55,56}. Due to improvements in the therapy and the growth and aging of the population, the prevalence of CAD is expected to rise^{28,55}.

2.2.2 The clinical burden of heart failure

Although the survival of HF patients improved over the last decades^{41,42,44}, mortality remains high¹⁸, with pooled one-, five-, and ten-year survival rates of 87%, 57%, and 35%, respectively⁵⁷. In addition, HF patients are at high risk of (recurrent) hospitalization, with patients being hospitalized once a year on average^{58,59}. As a sign of disease progression², hospitalizations are associated with an increased risk of rehospitalization and death in the first months after discharge and with each additional admission^{60–62}. In Germany, HF is one of the most common causes of death⁶³ and the most common diagnosis of hospital admissions⁶⁴.

In addition to multiple hospitalizations and a high mortality, HF patients suffer from manifold symptoms, such as breathlessness, fatigue, ankle swelling, and depression³. These symptoms interfere with the patients' daily life (e.g., functional limitation)^{65–67}, leading to a reduced quality of life of HF patients compared with the general population and patients with other chronic diseases^{68–70}. Women tend to present with more severe HF symptoms than

men^{24,71}. In addition, they report a lower quality of life, with more physical limitations and higher rates of anxiety and depression compared with men^{23,71–73}.

2.2.3 The economic burden of heart failure

While economic studies on HF costs are heterogenous regarding i) the definition of HF, ii) the analysis approach (i.e., incidence-based or prevalence-based), and iii) the costs considered (e.g., direct costs related to the healthcare provision, indirect costs related to productivity loss), all conclude a high economic burden of HF on healthcare systems^{74,75}. Recent estimates on HF costs reach up to more than \$300 billion (2017 and 2021) worldwide^{53,76} and €9.2 billion (2023) in Germany⁷⁷. In line with the increasing HF prevalence, this burden is expected to grow further¹⁸. For example, a 2.5-fold increase of HF expenditures is expected for the U.S. between 2012 and 2030, with a highest increase in patients aged >65 years^{18,78}.

Annual costs per HF patient show geographical variation, ranging from 900\$ in South Korea to 25,500\$ in Germany (2016 \$US)⁷⁵. Due to the multiple hospitalizations, main driver of HF costs is inpatient care, accounting for 44 to 96% of the overall costs^{74,75,79}. HF costs increase with disease severity and prevalence of comorbidities. For example, patients with NYHA IV caused 71% higher costs than those with NYHA I in a German cohort study⁷⁹. In addition, kidney dysfunction and diabetes mellitus are among the most common reasons of increasing HF costs, resulting in up to 0.5 times higher costs⁷⁵. Furthermore, while HF costs are stable and relatively low during the chronic disease state, costs are particularly high in the first year after diagnosis and at the end of life⁷⁵.

In conclusion, HF is a progressive disease that is associated with a significant clinical and economic burden. Since this burden is expected to rise with an increasing HF prevalence, HF prevention is gaining increasing importance.

2.3 Screening for and prevention of heart failure

2.3.1 Prevention of heart failure

Prevention in public health is commonly classified into four levels: i) primordial prevention or health promotion - prevention of risk factors; ii) primary prevention - prevention of the disease onset in patients at risk; iii) secondary prevention - prevention of disease-related events in patients having the disease; iv) tertiary prevention - prevention of progression or complications in

patients having the disease⁸⁰. While HF management has so far focused on secondary and tertiary prevention in patients with symptomatic HF (stage C and D), primary prevention in patients with risk factors (stage A) and, in particular, pre-HF (stage B) becomes increasingly important and was included in U.S. CPGs^{6,81}. It may result in less patients progressing to symptomatic HF (stages C and D) with irreversible cardiac damage⁸².

Several effective prevention measures are available for pre-HF patients, including targeted risk factor management, lifestyle adaptations, and pharmaceutical treatment^{6,81}. In particular, an optimized blood pressure, blood cholesterol, and diabetes management according to current CPGs is important^{6,81}. For example, based on data from a meta-analysis, a 5 mmHg systolic blood pressure reduction was associated with a significantly reduced risk of HF^{81,83}. In addition, a healthy diet, regular physical activity, avoiding overweight/obesity, and not smoking are key features in reducing the HF risk^{6,84,85}. For example, an optimal or average status of the AHA Life's Simple 7 health behaviors and factors (e.g., never smoker, body mass index <25 kg/m²) was associated with a significantly lower HF risk than a poor status⁸⁶. Lifestyle interventions therefore appear to be an important component for HF prevention⁸¹. Pharmaceutical approaches include beta blockers (BB), statins, angiotensin-converting-enzyme (ACE) inhibitors, and angiotensin II receptor blockers (ARBs). However, these are indicated only for patients with reduced LVEF ($\leq 40\%$), since evidence for patients with preserved LVEF remains limited so far⁶.

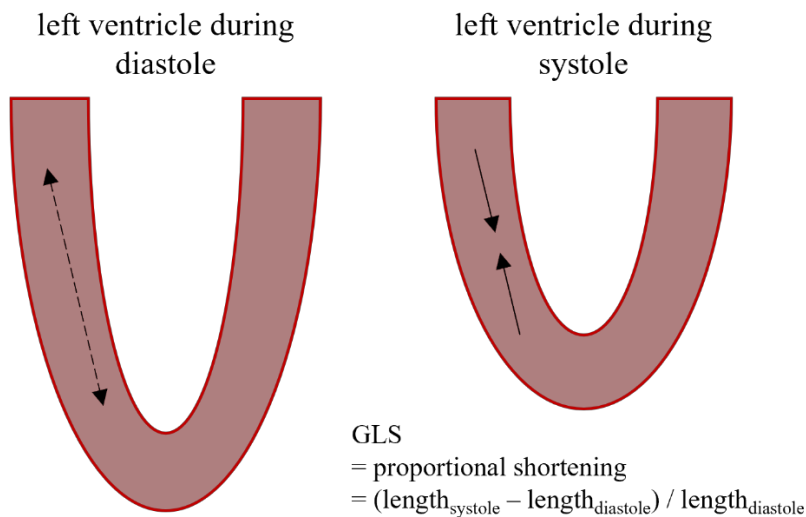
2.3.2 Screening for pre-heart failure

The diagnostic pathway of HF is usually initiated at the onset of typical symptoms (stage C/D HF)⁸⁷. To detect patients with pre-HF (stage B HF) and prevent the onset of HF, structured screening is essential. Since HF is a globally important disease¹⁸ with a recognizable asymptomatic stage (pre-HF)⁶, increasing knowledge about the natural progression^{8–10}, and evidence-based preventive measures⁶, several of the classic screening criteria are fulfilled^{88,89}. However, the optimal approach is still being investigated, with no established screening yet in clinical practice^{6,90}.

Screening for pre-HF can be based on different objective markers of pre-HF, such as reduced left ventricular systolic function, reduced strain, ventricular hypertrophy, elevated filling pressures, and increased levels of B-type natriuretic peptide (BNP)^{1,6}. Current CPGs recommend a screening based on BNP or N-terminal pro-B-type natriuretic peptide (NT-proBNP) in patients at risk of HF, since this may cost-effectively reduce the combined rates of left ventricular dysfunction and HF^{6,91,92}.

However, cardiac imaging parameters enable a direct assessment of the heart, and some can even detect subtle cardiac damage^{6,11}. Among numerous imaging parameters, the global longitudinal strain (GLS) may be a promising marker for HF screening⁹³. The GLS is a functional parameter that describes the extent of the heart's contraction in longitudinal direction during systole⁹⁴ (Figure 1, adapted from Chong et al., 2014⁹⁵). It is expressed as reduced proportion of the diastolic length of the left ventricle (i.e., negative value) with lower absolute values representing limited systolic function⁹⁴. Assessing the GLS allows the identification of even subtle impairments of the left ventricular function^{94,96–99}. Thereby, the GLS seems to be more reproducible and stable than the LVEF^{94,99,100}, the common marker of left ventricular dysfunction^{6,98}, and has an incremental prognostic value for cardiovascular morbidity and mortality to the LVEF^{96–98,100–102}. In addition, the GLS was proven as precise predictor of HF^{103,104}, with a stronger association in men than in women¹⁰⁵.

Figure 1: Schematic representation of the GLS (adapted from Chong et al., 2014⁹⁵)



GLS = Global Longitudinal Strain

The GLS can be determined using either echocardiography (ECHO) or cardiac magnetic resonance (CMR) imaging with an overall good agreement^{94,106}. While ECHO is widely available, less costly, and has fewer contraindications, CMR is nowadays the gold-standard imaging method for assessing heart function^{99,107–109}. For CMR strain analysis, accuracy, high feasibility, and good reproducibility were confirmed^{106,107,109}. In addition, compared with ECHO, it is associated with a larger field of view and good data acquisition independent of the body type, which enables a reliable GLS assessment even in difficult echocardiographic conditions (e.g., in obese patients)^{106,107,109}. Furthermore, recent developments towards semi-automatic strain

analysis mitigate the major disadvantage of a prolonged acquisition time¹⁰⁷. Despite these advantages, the potential of a GLS-based screening (via CMR) for early detection of pre-HF and HF prevention has yet to be established⁹³.

2.3.3 The importance of cost-effectiveness

In addition to the medical aim of health promotion, screening also pursues an economic aim of sparing resources (e.g., as a result of less patients to be treated)⁸⁸. However, while screening is commonly expected to be cost-saving by preventing (severe) disease, the treatment costs saved often do not offset the screening and prevention costs per detected case^{88,110}. For example, in a GLS-based pre-HF screening program, the costs of the GLS assessment and preventive measures for screen-detected patients might be higher than the treatment costs saved by delaying or preventing the progression to symptomatic HF.

Given the limited resources in healthcare systems, offering a pre-HF screening program inevitably means that these resources are no longer available for alternative services (e.g., CAD treatment)¹¹¹. Thus, as for every other healthcare service, a comprehensive analysis of benefits, harms, and costs of a pre-HF screening program is essential for allocation decisions¹¹⁰.

Health economic evaluations provide a structured approach that can inform allocation decisions on how resources should be spent to maximize the benefit. Therefore, they identify those healthcare interventions that provide the greatest benefit relative to their costs (i.e., the most cost-effective) from the relevant perspective (e.g., healthcare sector, payer, society^{112,113})^{111,114,115}. In particular, they can compare the clinical and economic consequences of a GLS-based pre-HF screening program to those of standard of care (SoC) by calculating the difference in costs (i.e., incremental costs) and benefits (i.e., incremental benefits)¹¹¹.

2.3.4 The importance of guideline adherence

Both the medical aim (i.e., health promotion) and the economic aim (i.e., cost-effectiveness) of screening programs can only be realized if detected patients receive evidence-based care that improves their prognosis^{88,116}. CPGs synthesize the best available evidence and assess benefits and harms of alternative care options. Based on this, they provide recommendations on appropriate care to support healthcare providers' and patients' clinical decision making. This should reduce practice variation and improve the quality of healthcare^{117,118}. For HF prevention, for example, the AHA guideline for HF management provides recommendations for risk factor management, lifestyle adaptations, and pharmaceutical therapy in stage A and B HF (chapter

2.3.1)⁶. A high adherence to well-developed CPGs may optimize clinical care and improve patient outcomes^{11,117,119,120}. For example, improved survival and readmission rates were observed for HF patients treated in line with CPGs^{121–123}.

According to this, a high adherence to CPGs for pre-HF management could significantly contribute to the success of a pre-HF screening program. In contrast, if screen-detected pre-HF patients do not receive recommended risk factor management and pharmaceutical therapy or do not follow evidence-based lifestyle adaptations, the reduction in HF risk is limited.

Similarly, guideline-adherent management of causative risk factors may improve HF prevention even if pre-HF is unknown. For example, a statins therapy in CAD patients as recommended in CPGs can reduce atherosclerotic plaque, MIs, and ultimately, the risk of HF^{27,81}. A prompt initiation of this management may be ensured by a timely and guideline-adherent diagnostic work-up in patients with suspected CAD.

Furthermore, guideline-adherent management of patients at risk of HF might have a positive economic impact. For example, the ENLIGHT-KHK trial observed a 26% healthcare providers' adherence to the German National Disease Management Guideline (GNDMG) for chronic CAD of 2019 for the use of invasive coronary angiography (CA) in the diagnostic work-up of chronic CAD in German non-university hospitals. This was associated with marginal more major adverse events and an additional expenditure for the German Statutory Health Insurance (SHI) compared with optimal (i.e., 100%) guideline adherence¹²⁴.

For these reasons, several European medical associations (e.g., European Society of Cardiology (ESC)) support the implementation of prevention guidelines in primary healthcare and discuss potential approaches for enhancing guideline adherence¹²⁰.

Besides ensuring overall guideline adherence, preventing differences in guideline-adherent care between patients is important, since these may have a negative effect on clinical outcomes. For example, increasing evidence shows a lower healthcare providers' guideline adherence for the management of ACS and the pharmaceutical therapy for stable CAD in women than men^{125–129}, which may partially explain their higher risk of death and MI^{125,126}.

With regard to HF prevention, a lower guideline adherence in women compared with men at risk might result in a higher probability of HF onset. Analyses on sex differences in guideline adherence and its predictors in patients at risk of HF could provide insights into disparities in guideline implementation and support targeted interventions to improve HF prevention.

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Chapter 3

Aims and objectives

3 Aims and objectives

This cumulative dissertation aims at exploring opportunities and challenges associated with the prevention of HF, and providing evidence to inform decision-making on the implementation of a structured GLS-based pre-HF screening program in the German healthcare system. Therefore, it comprises three DPs. By relating to various determinants of HF prevention (i.e., early detection of pre-HF, cost-effectiveness of a structured pre-HF screening program, guideline-adherent care of patients at risk of HF), and using various methods of analysis (i.e., descriptive statistics, weighted comparison of means, health economic modelling, regression analysis), these address the following objectives:

DP I: To estimate the pre-HF prevalence in a German at-risk population, and investigate the potential of a structured GLS-based screening program for early detection of pre-HF compared with SoC.

DP II: To assess the long-term cost-effectiveness of a GLS-based screening program for pre-HF compared with SoC from the perspective of the German SHI.

DP III: To investigate patient-related sex differences in healthcare providers' guideline adherence for invasive CA in patients with suspected CCS.

Chapter 4

Methods

4 Methods

4.1 DP I: Prevalence and early detection of pre-heart failure

DP I was embedded in the HERZCHECK trial (2020-2024), a cross-sectional study with an integrated randomized controlled trial (RCT) that evaluated a GLS-based screening program for pre-HF in a German at-risk population (ClinicalTrials.gov identifier: NCT05122793). The trial was set up in structurally underserved regions in Mecklenburg-Western Pomerania and Brandenburg in north-east Germany¹. It enrolled 4,666² women and men aged 40-69 years without HF symptoms, but with at least one pre-defined risk factor (diagnosis of hypercholesterolemia/arterial hypertension/obesity/diabetes mellitus/chronic kidney disease or tobacco consumption)¹.

All participants underwent a stress- and contrast-agent-free CMR examination in a fully mobile CMR unit with GLS assessment via semi-automatic feature tracking. In addition, participants received a laboratory testing and vital parameter assessment, and were asked to rate their health-related quality of life using standardized questionnaires. After being screened, participants were stratified into no pre-HF ($\text{GLS} < -15\%$), moderate pre-HF ($-15\% \leq \text{GLS} < -11\%$), and severe pre-HF ($\text{GLS} \geq -11\%$). All participants with pre-HF and 10% of those without pre-HF were subsequently included in the RCT comparing preventive measures (i.e., innovative patient-friendly medical report with GLS-information and recommendations for lifestyle adaptations and therapy; smartphone app for patients to monitor vital parameters; option of expert consultation for physicians) to SoC and were followed for 12 months. Primary endpoints were the prevalence of pre-HF, defined as $\text{GLS} \geq -15\%$ (cross-sectional study), and the effectiveness of the preventive measures compared with SoC, defined as difference in the GLS-change at 12 months follow-up (RCT)¹.

DP I comprised the assessment of the pre-HF prevalence (primary endpoint of the cross-sectional study) and two claims data analyses evaluating a) whether a GLS-based screening program could detect pre-HF significantly earlier before a HF would have been diagnosed in SoC (secondary endpoint of the cross-sectional study), and b) differences in adverse events (i.e., all-cause mortality, HF events, HF hospitalization) within the 12 months follow-up between participants with and without pre-HF². Figure 2 presents an overview of the datasets used in the different analyses.

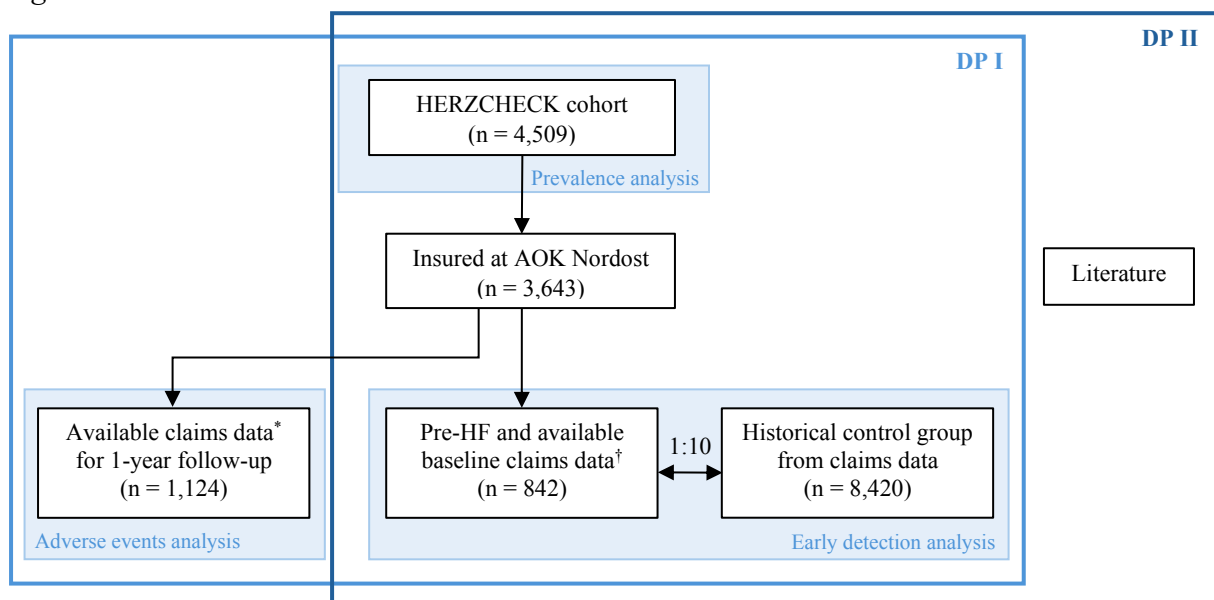
The analysis on early detection included claims data of i) prevalent pre-HF participants who were insured at the participating sickness fund, and, as the HERZCHECK trial was limited to 12-months follow-up, ii) a historical control group without HF obtained from 2013 claims

data of the participating sickness fund^{1,2}. To ensure comparability between the groups' cardiovascular risk profiles, first, the control group was constructed by matching 10 persons to each HERZCHECK participant. Matching criteria included the age group, sex, region of residence, and presence of at least one risk factor documented in the claims data². In a second step, covariate balance was further optimized (i.e., comparability regarding additional characteristics such as comorbidities and costs) using entropy balancing^{2,3}. This data preprocessing method reweights characteristics to achieve covariate balance in observational studies with binary treatment. It effectively adjusts for systematic and random inequalities while retaining valuable information (i.e., avoiding elimination of uncommon cases)^{3,4}.

The historical control group was followed for 9 years (2014-2022) for incident HF. In addition to the difference between the age at pre-HF detection in HERZCHECK participants and the age at HF diagnosis in the historical control group, the HF incidence and mortality in the historical control group were calculated. Subgroup analyses were conducted to evaluate the impact of sex, age, region of residence, and pre-HF severity. Sensitivity analyses were performed to estimate the robustness of the results².

Differences in adverse events were examined using Kaplan-Meier survival analyses based on claims data of all HERZCHECK participants (with and without pre-HF) who were enrolled in the RCT and were insured at the participating sickness fund².

Figure 2: Data used in DP I and II



*Claims data were available for 10% of HERZCHECK participants with preserved GLS and all HERZCHECK participants with pre-HF, who were included in the RCT, were insured at the AOK Nordost, and gave consent².

†Claims data were available for all HERZCHECK participants with pre-HF, who were included in the RCT, were insured at the AOK Nordost, gave consent, and were eligible for the comparison to the historical control group².

DP = Dissertation Project, HF = Heart Failure

4.2 DP II: Health economic consequences of screening for pre-heart failure

DP II was a decision-analytic (i.e., model-based) health economic evaluation of a GLS-based pre-HF screening program compared with SoC from the perspective of the German SHI, as pre-specified in the HERZCHECK trial¹. Compared with evaluations conducted alongside a trial, decision-analytic evaluations compare expected costs and benefits of different strategies under uncertainty by approximating and mathematically modelling the clinical situation with data from different sources (e.g., clinical trials, registries, claims data, quality of life data)^{5–8}.

Since HF is a chronic disease with recurring events, and effects of screening programs occur in the long term, a state-transition model (STM) was used^{5,8–10}. The STM divided the situation under consideration into mutually exclusive health states that are (clinically or economically) relevant for the decision context^{5,8,9,11}. In particular, pre-HF, HF without hospitalization, HF hospitalization, and death were differentiated¹². To evaluate costs and benefits of the strategies, the states were assigned costs and benefits corresponding to the decision-making context (i.e., state values)^{5,8,9,11}. Over fixed time intervals (i.e., monthly cycles) in the lifetime model¹², patients passed through the different health states and accumulated costs and benefits according to the strategy they were assigned^{5,8,9,11}. Thereby, pre-HF was assumed to remain unrecognized in the SoC-arm, whereas identified pre-HF patients in the screening-arm received preventive lifestyle interventions. Input parameters were obtained from the HERZCHECK trial, German public statistics, and published evidence (see Figure 2)¹².

When simulating a specific patient cohort (known as Markov model), transition probabilities depend only on the current health state without considering the patient's history^{9,11}. To overcome this so-called no-memory assumption, the STM was conducted as individual patient-level simulation (known as microsimulation)^{5,6,9,11} of 50,000 patients with screen-detected pre-HF¹². By simulating one individual at a time moving through the model, this allowed to take into account individual pathways of individuals from the target population^{5,9,11,13}. Therefore, age-, sex-, and GLS-dependent risks^{14,15} could be applied¹². In addition, the progressive nature of HF was reflected by applying risks based on the patient's previous hospitalizations^{12,16,17}.

Averaging the accumulated individual costs and benefits of all simulated individuals resulted in the expected costs and benefits of the strategies^{5,9,13}. By measuring the effectiveness as life years (LYs) and quality-adjusted life years (QALYs)¹², a cost-effectiveness analysis (i.e., cost per natural unit of benefit) and a cost-utility analysis (i.e., cost per quality-adjusted outcome)^{5,10,18} were conducted¹².

The screening program and SoC were compared by calculating an incremental cost-effectiveness ratio (ICER)^{5,10,19,20}:

$$ICER = \frac{(costs\ of\ screening - costs\ of\ SoC)}{(effectiveness\ of\ screening - effectiveness\ of\ SoC)}$$

To inform a decision, the ICER was compared with the decision-makers' willingness-to-pay (WTP)¹², with a decision in favor of the screening program if the WTP was higher than the ICER^{5,10,20}. Subgroup analyses investigated differences in the results according to patients' sex and age¹².

To estimate the uncertainty around the results and the decision to be made, deterministic and probabilistic sensitivity analyses^{5,8,19} were conducted¹². In a deterministic sensitivity analysis, input parameters and assumptions were varied individually, while all other parameters were kept constant^{5,6,12,19}. Since the parameters are usually not independent of one another, all parameters were also varied simultaneously in a probabilistic sensitivity analysis. In particular, the model was run 1,000 times with each time a new set of input values (one for each parameter) randomly drawn from pre-defined probability distributions of the parameters^{5,12,19}. Furthermore, the model was validated by consulting clinical experts, comparing to published evidence, and ensuring technical accuracy^{12,21}.

An extended model took into account the expected value of patients' opportunity to benefit from future innovations in their extended life¹². This option value (OV)²² may result from a prolonged survival or a slowdown in the disease progression²³, and should be considered in the value assessment of health technologies²². It was implemented in the decision-analytic model by forecasting trends in mortality and morbidity (trend approach)^{12,23}. To evaluate the impact of the OV, the incremental change in benefits (i.e., incremental OV) compared with the basic model was calculated¹². In addition, the costs of medical advancement were considered in the OV model and the incremental costs compared with the basic model were calculated¹².

4.3 DP III: Sex differences in guideline adherence for suspected coronary artery disease

DP III was a regression analysis that evaluated the difference in the healthcare providers' guideline adherence for CA between women and men with suspected CCS and in the predictors between both sexes²⁴. It was a pre-specified sub-analysis of the German ENLIGHT-KHK trial, a multicenter, prospective observational study that evaluated the guideline adherence of CA-use

in the diagnostic work-up of suspected CCS and the resulting health economic consequences (German Clinical Trials Register DRKS00015638, Registered 19.02.2019; Universal Trial Number (UTN): U1111-1227-8055). Between 2019 and 2021, a total of 901 women and men with suspected CCS without ACS were enrolled, who were assigned to or underwent a CA at one of nine non-university hospitals in Germany. Primary outcome of the trial was the adherence to the GNDMG for chronic CAD of 2019²⁵.

The regression analysis included all participants with available data on the providers' adherence to the GNDMG for chronic CAD of 2019^{24,26}. Sex differences in guideline adherence were evaluated by comparing the extent of guideline adherence in women and men. In addition, the association between patient sex and the healthcare providers' guideline adherence was examined using multiple binary logistic regression models. To investigate differences in predictors of guideline adherence, the regression models were run separately for women and men. Covariates were selected in consultation with a clinical expert and included non-invasive testing and its results, age, symptoms, risk factors, and comorbidities. All data were obtained from the ENLIGHT-KHK trial²⁴.

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Chapter 5

Scientific publications

5 Scientific publications

5.1 DP I: Prevalence and early detection of pre-heart failure

The article presented in this chapter has been previously published in ‘Circulation: Heart Failure’ (2026, 19:e013935, doi:10.1161/CIRCHEARTFAILURE.125.013935).

HERZCHECK: Early Detection of Subclinical Heart Failure Using Mobile Cardiac Magnetic Resonance and Telemedicine in Rural and Underresourced Regions

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ORIGINAL ARTICLE



HERZCHECK: Early Detection of Subclinical Heart Failure Using Mobile Cardiac Magnetic Resonance and Telemedicine in Rural and Underresourced Regions

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BACKGROUND: There is a growing consensus that screening for subclinical preheart failure (HF) may reduce the burden of symptomatic HF by allowing for timely preventive interventions. However, validated screening algorithms are currently lacking. The aim of this study was to evaluate a fully mobile telemedically supervised cardiac magnetic resonance, as a simple standardized, and ubiquitously applicable screening algorithm for subclinical pre-HF in rural and underresourced regions.

METHODS: HERZCHECK was a cross-sectional cohort study conducted at 12 sites across rural and underresourced regions of Germany. Asymptomatic participants (40–69 years) with ≥ 1 cardiovascular risk factor—obesity, smoking, arterial hypertension, diabetes, hypercholesterolemia, or chronic kidney disease—were enrolled and underwent telemedically supervised contrast-free short cardiac magnetic resonance in mobile screening units. Subclinical pre-HF was diagnosed using a predefined cutoff of global longitudinal strain $\geq -15\%$. A matched and entropy-balanced control cohort constructed from claims data was used to determine the time difference between detection of subclinical pre-HF in HERZCHECK and the first symptom-based diagnosis of HF within the standard of care.

RESULTS: Between June 2021 and April 2023, 4666 participants were enrolled in the study, of which 4509 participants were included in the final analysis. The prevalence of subclinical pre-HF in the studied at-risk population was 22.7% (95% CI, 21.5%–23.9%). Global longitudinal strain-based screening identified subclinical pre-HF 6.7 years before the average onset of symptomatic HF within the standard of care ($n=8420$).

CONCLUSIONS: Subclinical pre-HF affects approximately one-fourth of the at-risk population in rural and underresourced regions. The HERZCHECK approach identifies patients suitable for targeted preventive interventions ≈ 7 years earlier than the standard of care.

REGISTRATION: URL: <https://www.clinicaltrials.gov>; Unique identifier: NCT05122793.

Key Words: cardiovascular diseases ■ heart failure ■ magnetic resonance imaging ■ mobile health units ■ risk factors ■ sprains and strains ■ telemedicine

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WHAT IS NEW?

- HERZCHECK demonstrates the feasibility of a standardized, fully mobile and telemedicine-supervised cardiac magnetic resonance-based screening approach using global longitudinal strain as a scalable end point to detect subclinical pre-heart failure (HF).
- Systematic application of this strategy identifies subclinical pre-HF in 22.7% of the rural at-risk population and ≈7 years earlier than the diagnosis of symptomatic HF under the current standard of care.

WHAT ARE THE CLINICAL IMPLICATIONS?

- On-demand mobile and telemedicine-supervised cardiac magnetic resonance might support the clinical needs of patients in rural and underresourced areas to improve healthcare and support local physicians.
- Integration of innovative systematic screening into routine care could substantially advance the timely identification of subclinical pre-HF and enable earlier initiation of strategies to prevent progression to symptomatic disease.
- Given the current lack of consensus, further studies are required to define the optimal management of subclinical pre-HF and to determine whether the diagnostic lead time achieved ultimately translates into improved clinical outcomes.

Nonstandard Abbreviations and Acronyms

CMR	cardiac magnetic resonance
GLS	global longitudinal strain
HF	heart failure
LVEF	left ventricular ejection fraction
NT-proBNP	N-terminal pro-B-type natriuretic peptide

Strategies to reduce the socioeconomic burden of heart failure (HF) are much sought after, especially in rural and underresourced regions affected by a strong imbalance between high prevalence and insufficient access to specialized healthcare resources.^{1,2} Results from the STOP-HF and PONTIAC trials suggest that the early identification of subclinical pre-HF among at-risk patients reduces the incidence of clinically manifest HF by allowing for timely, targeted preventive interventions.^{3,4} However, suitable standardized screening approaches are currently unavailable in clinical routine care.

Signs of systolic dysfunction may be the optimal screening target, as indicated by a meta-analysis involving >25 000 participants, which revealed that asymptomatic

left ventricular systolic dysfunction is associated with an almost 5-fold relative risk of transitioning to clinically manifest HF in maximally adjusted models.⁵ Although being the classic domain of the left ventricular ejection fraction (LVEF), myocardial deformation imaging has emerged as a more robust, reproducible, and sensitive method to detect subtle alterations in systolic function. Among the different myocardial deformation indices, recent evidence suggests that left ventricular global longitudinal strain (GLS), in particular, is a precise predictor of incident HF among the general or at-risk population.^{6–8} Consequently, GLS appears to be a promising marker to identify subclinical pre-HF and guide targeted lifestyle or pharmacological interventions to prevent the transition to clinically manifest HF.

Leveraging these favorable characteristics of GLS, HERZCHECK sought to accurately determine the prevalence of subclinical pre-HF in an at-risk population and to assess whether GLS can improve the early detection of patients who develop clinically manifest HF when utilized as part of a standardized screening routine. Through the use of mobile, telemedically supervised cardiac magnetic resonance (CMR) units, the evaluated screening routine was specifically developed as an innovative solution to address the needs of rural and underresourced regions while ensuring maximum diagnostic accuracy and reproducibility.

METHODS

Data Availability

The data supporting the findings of this study are not openly available but may be shared upon reasonable request to the corresponding author and with the approval of the HERZCHECK consortium. Data will only be shared with academic institutions after signing a data-sharing agreement.

Study Design and Participants

HERZCHECK was an investigator-initiated, cross-sectional cohort study with an integrated prospective randomized controlled trial that was conducted at 12 sites across rural and underresourced regions in Germany under telemedical supervision of the Deutsches Herzzentrum der Charité between October 2020 and September 2024. Regions were classified as rural and underresourced based on the official definition used by the German Federal Ministry of Education and Research.⁹ The study was approved by the ethics committee of the Charité-Universitätsmedizin Berlin, Germany (EA4/204/20), registered on ClinicalTrials.gov (REGISTRATION: URL: <https://www.clinicaltrials.gov>; Unique identifier: NCT05122793), and conducted in accordance with the Declaration of Helsinki and relevant guidelines for good clinical practice. All participants provided written informed consent before inclusion in the study. A comprehensive summary of the study protocol has previously been published.¹⁰

The herein presented cross-sectional cohort study had 2 primary objectives: first, to accurately determine the prevalence

of subclinical pre-HF by the criterion of a reduced GLS in a representative at-risk population residing in rural and underresourced regions in Germany; and second, to test the hypothesis that a standardized systematic GLS-based screening enables the identification of patients who develop HF significantly earlier than symptomatic HF would have been diagnosed within the current standard of care. Additional exploratory objectives were to assess the association between specific risk factor constellations and the prevalence of subclinical pre-HF, as well as the association of subclinical pre-HF with adverse events.

To determine the prevalence of subclinical pre-HF, consecutive individuals presenting to 1 of the 12 study sites were assessed for eligibility for participation by a study physician via telemedical consultation. Individuals between 40 and 69 years of age and with existing statutory health insurance were eligible to participate in HERZCHECK if they had at least one of the following modifiable cardiovascular risk factors: hypercholesterolemia, arterial hypertension, obesity, smoking/tobacco consumption, chronic diabetes, or chronic kidney disease. Individuals were excluded if they had previously diagnosed HF or symptoms related to HF. Upon inclusion in the study, all participants underwent contrast- and stress-agent-free CMR. Subclinical pre-HF was diagnosed using a previously defined cutoff of the GLS (ie, $\text{GLS} \geq -15\%$).¹¹ Additional baseline examinations included a standardized medical history, validated quality-of-life questionnaires, and laboratory testing.

The potential of the proposed GLS-based screening to enable the identification of patients with subclinical pre-HF earlier than the onset of symptomatic HF within the standard of care was assessed by comparing a subgroup of the HERZCHECK cohort, including participants diagnosed with subclinical pre-HF, with a control cohort constructed from claims data of a major health insurance company in Germany (AOK Nordost – Die Gesundheitskasse, Potsdam, Germany). To be eligible for inclusion in the HERZCHECK subgroup, participants had to be insured with the same aforementioned health insurance company, reside in Mecklenburg-Pomerania or Brandenburg at the end of the year in which the CMR was performed, and have consented to the analysis of their claims data. Initial matching (1:10) and subsequent entropy balancing (details provided as [Supplemental Methods S1](#) and [Table S1](#)) were conducted to ensure comparability of the control cohort with the HERZCHECK subgroup regarding cardiovascular risk profile. Additional approval for the use of the claims data was obtained from the ethics committee of the University of Cologne, Germany (EA23-1238).

Procedures

The following provides comprehensive descriptions of the study procedures that are of central relevance for the interpretation of the data reported in this article. Details regarding all other study procedures, including a telemedical consultation to collect participant-reported data on sex, medical history, and current medication, on-site measurement of vital parameters, a blood draw for laboratory testing, and self-administered quality-of-life questionnaires, have previously been published.¹⁰

Cardiac Magnetic Resonance

All participants in the HERZCHECK cohort underwent a stress- and contrast-agent-free CMR exam that was performed by an extensively trained CMR technician in a fully mobile CMR unit

equipped with a 1.5T Philips Ingenia dStream scanner (Philips Healthcare, Best, the Netherlands). The standardized protocol was designed according to current recommendations of the Society of Cardiac Magnetic Resonance and included a survey in 3 dimensions, short-axis, 2-, 3-, and 4-chamber cine sequences, as well as T1- and T2-mapping sequences. Images were sent to the Deutsches Herzzentrum der Charité, where they were analyzed offline by experienced Society of Cardiac Magnetic Resonance-certified study investigators using cvi42, version 5.13.7 (Circle Cardiovascular Imaging, Inc, Calgary, Canada). Left ventricular volumes and function were quantified from the full short-axis stack following current Society of Cardiac Magnetic Resonance consensus recommendations for the standardized image interpretation and postprocessing in CMR.¹² T1- and T2-relaxation times were measured in the midventricular septum. Semiautomatic feature tracking was used to analyze the GLS from 3 long-axis views, with manual selection of identical end-diastolic and end-systolic phases across short-axis and long-axis slices. When automated contours did not correctly align with the endocardial and epicardial borders, delineation was adjusted to ensure exclusion of trabeculae and papillary muscles. Incomplete CMR data sets precluding valid analysis of the GLS led to exclusion of the respective participant from further analyses.¹⁰

Identification of Adverse Events in the HERZCHECK Cohort

In line with the integrated randomized controlled trial, all participants from the HERZCHECK cohort who were diagnosed with subclinical pre-HF and 10% of those with preserved GLS were followed for 12 months using structured questionnaires.¹⁰ In addition, for a subgroup of participants insured with the cooperating health insurance provider (AOK Nordost–Die Gesundheitskasse, Potsdam, Germany), claims data for each participant's specific period of 24 months before and 12 months after baseline (minimum 9 months for outpatient visits) were available. Based on this, adverse events within 12 months after baseline could be investigated. Adverse events considered for this analysis included all-cause death, HF-related hospitalizations, and HF-related events (composite of HF-related hospitalizations and outpatient events). The respective definitions are provided as [Supplemental Methods S2](#).

Quantification of Time Gained for Prevention of Symptomatic HF

To quantify the time gained for prevention of symptomatic HF, the difference between the age at subclinical pre-HF detection (ie, date of CMR with impaired GLS) in participants of the HERZCHECK cohort and the age at first symptomatic HF diagnosis in the matched (1:10) and entropy-balanced control cohort was analyzed (details provided as [Supplemental Methods S3](#)). The age at HF detection in the control cohort was defined as the age at first validated diagnosis of incident HF, as documented in claims data spanning a 9-year observation period (2014–2022). The respective definitions of the diagnoses qualifying as validated incident HF are summarized in [Supplemental Methods S4](#). The frequency and incidence rate per 1000 patient years of symptomatic HF in the control cohort were also calculated.

Statistical Analysis

Statistical analyses were conducted on data from all eligible participants extracted after database lock using R, version

4.3.3 or higher (R Foundation for Statistical Computing, Vienna, Austria). Continuous and categorical data are presented as mean $\pm$ SD and counts with corresponding percentages, respectively. Effect measures are given with corresponding 95% CIs. All hypothesis tests were performed 2-sided at a significance level of 5%.

To determine the prevalence of subclinical pre-HF, the proportion of participants with GLS $\geq$ -15% is reported along with Clopper-Pearson 95% CIs. With the sample size of 4509 participants, an accuracy (half-width of the 95% CI) of $\pm$ 1% at an assumed prevalence of 20% of subclinical pre-HF can be achieved. Dedicated sample size calculations have previously been published.¹⁰

Demographic data, as well as data pertaining to secondary or exploratory end points, are summarized for the entire cohort and compared between participants with subclinical pre-HF (ie, GLS $\geq$ -15%) and those with preserved GLS using *t* tests or χ^2 tests, as appropriate. Nonnormally distributed parameters reflecting concentrations (ie, NT-proBNP [N-terminal pro-B-type natriuretic peptide] and ferritin) were log-transformed beforehand. Secondary, exploratory, and safety outcomes were not adjusted for multiple testing due to their exploratory nature. Missing values were excluded from the analysis on a per-parameter basis and were not subject to imputation.

The association of individual self-reported cardiovascular risk factors (ie, inclusion criteria) with subclinical pre-HF by the criterion of GLS $\geq$ -15% was assessed using a multivariable logistic model including age decades (40–49 years, 50–59 years, 60–69 years), sex (female, male), obesity (yes, no), arterial hypertension (yes, no), diabetes (yes, no), hypercholesterolemia (yes, no), smoking (yes, no), and chronic kidney disease (yes, no) as covariates.

Adverse event-free survival was estimated for a subgroup of HERZCHECK participants with available claims data using Kaplan-Meier analyses. Differences in adverse event-free survival between participants with subclinical pre-HF and those with preserved GLS were assessed using log-rank tests (details provided as [Supplemental Methods S2](#)).

Analyses to quantify the time gained for prevention were performed on a subgroup of all HERZCHECK participants who were diagnosed with subclinical pre-HF and were insured with the cooperating health insurance provider (AOK Nordost–Die Gesundheitskasse, Potsdam, Germany), as well as the 1:10 matched and entropy-balanced control cohort. Baseline characteristics (obtained from claims data) are reported and were compared between the subgroup of HERZCHECK participants and the control cohort using absolute standardized mean differences. The frequency and incidence rate per 1000 patient-years of symptomatic HF in the control cohort were calculated based on available claims data. The time gained for prevention is reported as the mean difference with 95% CI between the age at detection of subclinical pre-HF in HERZCHECK and the age at first incident of symptomatic HF in the control cohort, with statistical significance being tested using a weighted *t* test (details provided as [Supplemental Methods S3](#)). Several sensitivity analyses and prespecified subgroup analyses according to sex, age, region of residence, and severity of GLS impairment were performed to assess the robustness of the obtained results (details provided as [Supplemental Methods S5](#)). The Benjamini-Hochberg procedure was applied to account for multiple testing.

Role of the Funding Source

The HERZCHECK trial was fully funded by the Innovation Fund for the promotion of new forms of care of the Federal Joint Committee (Gemeinsamer Bundesausschuss; Funding Reference: 01NVF19014). The funder of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

RESULTS

Between June 2021 and April 2023, 4784 individuals presenting to 1 of the 12 study sites were screened. After exclusion of 118 individuals who did not meet the eligibility criteria, 4666 participants were enrolled. Another 151 enrolled participants were excluded due to incomplete CMR examinations (*n*=139, claustrophobia; *n*=12, insufficient image quality), and 6 participants were excluded due to technical issues, resulting in a total of 4509 participants included in the final analysis (flow-chart provided as [Figure S1](#)).

Clinical characteristics of the HERZCHECK population are summarized in Table 1. Of all participants, 2511 (56%) were female and 1998 (44%) were male. The mean age was 60 $\pm$ 7 years. In descending order, the most common participant-reported cardiovascular risk factors at inclusion were arterial hypertension (74%; *n*=3349), smoking (59%; *n*=2633), hypercholesterolemia (47%; *n*=2101), obesity (44%; *n*=1989), diabetes (21%; *n*=957), and chronic kidney disease (5%; *n*=208). Notably, 2083 (46%) participants reported having $\geq$ 3 of the cardiovascular risk factors prespecified for inclusion. Only 296 (7%) and 154 (4%) participants reported a history of coronary heart disease or myocardial infarction, respectively.

With a GLS $\geq$ -15% being identified in a total of 1023 participants, the prevalence of subclinical pre-HF in the studied at-risk population was 22.7% (95% CI, 21.5%–23.9%; Figure 1). The prevalence of subclinical pre-HF was significantly higher in male participants compared with female participants (37% versus 12%; *P*<0.001) and slightly elevated in the highest age decade compared with younger participants (40–49 years, 21%; 50–59 years, 20%; 60–69 years, 25%; *P*=0.002). Regional variation in the prevalence of subclinical pre-HF is shown in [Figure S2](#), with the lowest and highest prevalence being 19% and 27%, respectively. Of those diagnosed with subclinical pre-HF by the criterion of an impaired GLS, 278 (32%) individuals had elevated NT-proBNP plasma levels (ie, $\geq$ 14.78 pmol/L), and 244 (24%) had a reduced LVEF (ie, <50%). Additional CMR findings, as well as data from laboratory tests and quality-of-life questionnaires, are summarized and compared between participants with and without subclinical pre-HF in Table 2. Cross-tables demonstrating the relationship between GLS-based subclinical pre-HF and elevated NT-proBNP or reduced LVEF are provided as [Tables S2 and S3](#). Notably, GLS-based subclinical pre-HF would

Table 1. Demographics of the HERZCHECK Cohort

	n	HERZCHECK cohort (n=4509)
Demographics		
Age, y	4509	60±7
Sex	4509	
Male		1998 (44%)
Female		2511 (56%)
Cardiovascular risk factors		
Arterial hypertension	4505	3349 (74%)
Hypercholesteremia	4505	2101 (47%)
Diabetes	4505	957 (21%)
Current or past smoker	4505	2633 (59%)
Obesity (BMI ≥30 kg/m ²)	4509	1989 (44%)
Chronic kidney disease	4505	208 (5%)
No. of risk factors	4505	
1–2		2422 (54%)
≥3		2083 (46%)
CAD	4341	296 (7%)
History of myocardial infarction	4341	154 (4%)
History of PCI	3084	160 (5%)
History of CABG	4337	31 (1%)
History of stroke	4327	186 (4%)
History of subjective arrhythmia	4326	500 (12%)
History of cancer	4451	435 (10%)
Medications		
ACE inhibitors	4469	1145 (30%)
Angiotensin receptor blockers	4469	1308 (34%)
ARNI	4469	5 (0%)
β-blockers	4469	1382 (36%)
Calcium channel blockers	4469	23 (1%)
MRA	4469	75 (2%)
Diuretics	4469	700 (17%)
Antiplatelets	4469	601 (13%)
Anticoagulants	4469	193 (4%)
Lipid-lowering therapy	4469	2110 (47%)
Insulin	4469	235 (6%)
Oral antidiabetics	4469	1139 (25%)
SGLT2 inhibitors	4469	206 (5%)

Demographics, self-reported cardiovascular risk factors and self-reported medication usage among the entire HERZCHECK cohort (n=4509). Continuous data are presented as mean±SD and categorical data are presented as numbers with corresponding percentages (%). ACE indicates angiotensin-converting enzyme; ARNI, angiotensin receptor-neprilysin inhibitor; BMI, body mass index; CAD, coronary artery disease; CABG, coronary artery bypass graft; MRA, mineralocorticoid receptor antagonist; PCI, percutaneous coronary intervention; and SGLT2, sodium-glucose co-transporter 2.

have been missed in 15.6% (n=586/3762) and 17.3% (n=779/4509) of all participants based on NT-proBNP or LVEF, respectively. A proportional Venn-diagram visualizing the relationship between impaired GLS-based subclinical pre-HF, elevated NT-proBNP and reduced LVEF is provided as Figure S4.

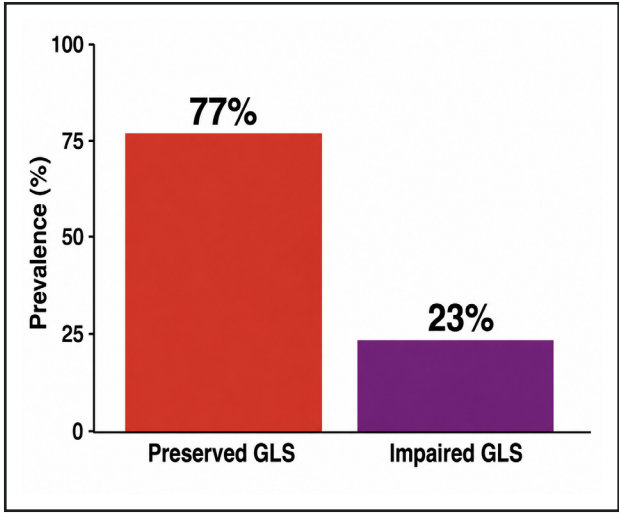


Figure 1. Overall prevalence of impaired global longitudinal strain (GLS).

Prevalence of preserved (77.3%; red bar) and impaired (22.7%; purple bar) GLS in the HERZCHECK cohort (n=4509).

Beyond male sex (odds ratio, 4.18 [95% CI, 3.58–4.89]; $P<0.001$), cardiovascular risk factors independently associated with the presence of subclinical pre-HF in the multivariable logistic regression analysis included smoking (odds ratio, 1.39 [95% CI, 1.19–1.63]; $P<0.001$), obesity (odds ratio, 1.49 [95% CI, 1.28–1.73]; $P<0.001$), and diabetes (odds ratio, 1.71 [95% CI, 1.44–2.04]; $P<0.001$). No significant independent associations with subclinical pre-HF were identified for increasing age decades, arterial hypertension, hypercholesterolemia, or chronic kidney disease (Figure S4). The observed prevalence of subclinical pre-HF in HERZCHECK participants with different cardiovascular risk factor constellations is reported in Figure 2.

Claims data for the 1-year follow-up period were available for 1124 HERZCHECK participants (n=878 with 12 months of data on outpatient events), including 282 with preserved GLS (n=221 with 12 months of data on outpatient events) and 842 with subclinical pre-HF (n=657 with 12 months of data on outpatient events). The 1-year incidence of all-cause death, HF-related hospitalizations, and HF-related events was 1% (n=11), 4% (n=43), and 15% (n=135), respectively (details provided as Table S4). No differences in overall survival were observed between those with preserved GLS and those with subclinical pre-HF ($P=0.22$). However, participants with subclinical pre-HF had a significantly increased risk of HF-related hospitalizations ($P=0.0017$). Kaplan-Meier curves illustrating these comparisons are presented in Figure 3 and Figure S5.

Of all participants in the HERZCHECK cohort diagnosed with subclinical pre-HF, 842 (82%) were eligible for inclusion in the subgroup that was compared against the control cohort (n=8420, ratio 1:10; flowchart provided as Figure S1). After entropy balancing, there were

Table 2. CMR, Laboratory, and HeartQoI Findings of the HERZCHECK Cohort

	n	Total cohort (N=4509)	Preserved GLS (n=3486)	Subclinical pre-HF (n=1023)	P value
CMR findings					
GLS (%)	4509	−17.02±2.31	−17.95±1.51	−13.84±1.61	<0.001
LVEF (%)	4509	60±6	62±5	54±7	<0.001
LVEF <50%	4509	289 (6%)	45 (1%)	244 (24%)	<0.001
LVEDV/BSA (mean)	4424	73±14	73±13	76±17	<0.001
LVEDV/BSA >108 mL/m ² (men) or >96 mL/m ² (women)	4424	99 (2%)	47 (1%)	52 (5%)	<0.001
LVESV/BSA (mean)	4463	30±9	28±7	36±12	<0.001
LVESV/BSA >47 mL/m ² (men) or >40 mL/m ² (women)	4463	209 (5%)	67 (2%)	142 (14%)	<0.001
LVEDD (mean)	4479	50.3±5.0	49.9±4.7	51.6±6.0	<0.001
LVEDD >58 mm (men) or >52 mm (women; HerzCheck)	4479	657 (14%)	487 (15%)	170 (16%)	<0.001
IVSd (mean)	4324	11.09±2.56	10.78±2.44	12.15±2.66	<0.001
IVSd ≥12 mm	4324	1434 (33%)	958 (29%)	476 (48%)	<0.001
Lateral wall (mean)	4496	7.34±1.53	7.12±1.43	8.10±1.65	<0.001
Lateral wall ≥12 mm	4496	47 (1%)	17 (1%)	30 (3%)	<0.001
LV myocardial mass/BSA (mean)	4454	48±9	46±8	54±10	<0.001
T1 time native (mean)	4451	1.029±33	1.027±32	1.035±35	<0.001
T1 time native >1073 ms	4451	208 (5%)	125 (4%)	83 (8%)	<0.001
T2 time native (mean)	4452	53.2±3.3	53.2±3.2	53.4±3.6	0.110
T2 time native >59 ms	4452	66 (2%)	39 (1%)	27 (3%)	<0.001
Laboratory findings					
NT-proBNP (log, pmol/L)	3762	2.30±0.81	2.27±0.73	2.41±1.01	<0.001
NT-proBNP (pmol/L)	3762	15.67±32.11	13.19±15.05	23.98±60.36	
NT-proBNP ≥14.78 pmol/L	3762	1108 (29%)	830 (29%)	278 (32%)	0.050
eGFR, mL/min	3682	100±20	99±20	105±22	<0.001
eGFR >90 mL/min	3682	2643 (72%)	1969 (69%)	674 (80%)	
eGFR 60–90 mL/min		929 (25%)	786 (28%)	143 (17%)	
eGFR <60 mL/min		110 (3%)	81 (3%)	29 (3%)	
HbA1c (mmol/mol)	3773	6.01±0.82	5.93±0.73	6.28±1.03	<0.001
HbA1c ≥6.5%		702 (19%)	439 (15%)	263 (30%)	
Total cholesterol, mmol/L	3765	5.39±1.22	5.49±1.21	5.08±1.22	<0.001
Total cholesterol >6.2 mmol/L		908 (24%)	753 (26%)	155 (18%)	
Triglycerides, mmol/L	3765	2.15±1.53	2.09±1.49	2.37±1.64	<0.001
Triglycerides >5.64 mmol/L		99 (3%)	70 (2%)	29 (3%)	
HDL-cholesterol, mmol/L	3765	1.48±0.44	1.53±0.43	1.33±0.41	
HDL-cholesterol >1.2 mmol/L		2680 (71%)	2200 (76%)	480 (58%)	
LDL-cholesterol, mmol/L	3765	3.62±1.20	3.68±1.20	3.40±1.18	<0.001
LDL-cholesterol, ≥1.8 and <2.6 mmol/L		549 (15%)	407 (14%)	142 (16%)	
LDL-cholesterol ≥2.6 and <3.0 mmol/L		398 (11%)	282 (10%)	116 (13%)	
LDL-cholesterol ≥3.0 mmol/L		2581 (69%)	2059 (71%)	522 (60%)	
Hemoglobin, mmol/L	3774	8.91±0.76	8.83±0.74	9.18±0.77	<0.001
Hemoglobin <7.45 mmol/L (women) or <8.07 mmol/L (men)		137 (4%)	110 (4%)	27 (3%)	
Ferritin, log; µg/L	3765	4.53±0.96	4.50±0.97	4.67±0.94	<0.001
Ferritin, µg/L	3765	140.76±142.42	136.19±141.74	150.06±143.70	
Transferrin saturation, %	3671	26±10	26±10	26±10	0.168
Ferritin <100 µg/L	3765	1902 (51%)	1522 (53%)	380 (44%)	<0.001
Ferritin=100–299 µg/L and Transferrin saturation <20%	3724	319 (9%)	238 (8%)	81 (10%)	<0.001

(Continued)

Table 2. Continued

	n	Total cohort (N=4509)	Preserved GLS (n=3486)	Subclinical pre-HF (n=1023)	P value
HeartQoL					
Physical	4236	2.25±0.69	2.28±0.67	2.16±0.75	<0.001
Emotional	4206	2.43±0.68	2.44±0.67	2.41±0.70	0.250
Global	4236	2.31±0.63	2.33±0.61	2.23±0.68	<0.001

Cardiac magnetic resonance, laboratory, and HeartQoL findings summarized for the entire HERZCHECK cohort (n=4509) and compared between those with preserved global longitudinal strain (n=3486) and those with subclinical preheart failure (ie, impaired global longitudinal strain; n=1023). Continuous data are presented as mean with SD and categorical data are presented as numbers with corresponding percentages (%). *P*<0.05 indicate statistical significance. BSA indicates body surface area; CMR, cardiac magnetic resonance; eGFR, estimated glomerular filtration rate; GLS, global longitudinal strain; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; HF, heart failure; IVSd, interventricular septal thickness at end-diastole; LDL, low-density lipoprotein; LV, left ventricular; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.

no differences in baseline characteristics between the HERZCHECK subgroup and the control cohort (absolute standardized mean difference <0.1 for all characteristics; comparisons of the baseline characteristics of both groups before and after entropy balancing are presented in Tables S5 and S6; Figure S6). Based on the available claims data spanning a 9-year observation period, a weighted 26% (n=2177) and 20% (n=1665) of the control cohort were diagnosed with symptomatic HF or died, respectively. At an overall weighted observation time of 60 457.9 patient-years (mean, 7.2±2.8 years/patient), this translated to a weighted HF incidence of 36.0 per 1000 patient-years.

The weighted mean age at diagnosis of subclinical pre-HF in the HERZCHECK subgroup and at HF incidence in the entropy-balanced control cohort was 60.9±7.0 years and 67.5±6.4 years, respectively. Thus, subclinical pre-HF in the HERZCHECK subgroup was detected 6.7 years (95% CI, 6.11–7.25 years; *P*<0.001) earlier than symptomatic HF in the entropy-balanced control cohort (Figure 4). Results from subgroup and sensitivity analyses after entropy balancing are reported in Tables S7 and S8. Results before entropy balancing are reported in Tables S9 and S10.

DISCUSSION

Whereas the concept of subclinical pre-HF (stage B HF) as a precursor of symptomatic HF is well established in US HF guidelines, it remains largely unrecognized in their European counterparts.^{13,14} Data from 2 randomized controlled trials demonstrated that early identification of subclinical pre-HF can reduce the incidence of symptomatic HF, if followed by targeted preventive interventions, and indicate that adopting a similar approach in routine clinical care for the at-risk population could have a significant beneficial impact on the immense socioeconomic burden of HF.^{3,4}

HERZCHECK herein presents the blueprint for a simple, standardized, GLS-based CMR screening approach for subclinical pre-HF that was developed based on previous evidence for the strong association

of impaired GLS with incident symptomatic HF, as well as the high accuracy and reproducibility of CMR, even in individuals with typically challenging acoustic conditions posing problems in echocardiography.^{5–8,15–17} Systematic application of this screening approach in a representative cohort of 4509 participants with established cardiovascular risk factors from rural and underresourced regions in Germany confirmed its feasibility and demonstrated that around 23% (ie, almost one-fourth) of the at-risk population has traceable signs of subclinical pre-HF.

These findings are of great importance, as current estimates of the prevalence of subclinical pre-HF are highly variable, depending on specific participant selection and the diagnostic criteria used. Although most available studies defined subclinical pre-HF more broadly, using different selections of the diagnostic criteria for stage B HF outlined in the US HF guidelines, Russo and colleagues previously reported the prevalence of subclinical pre-HF assessed solely by impairments in GLS. Using a numerically comparable GLS cutoff (ie, –14.7%), they reported a prevalence of impaired GLS of 16.8% among those with preserved LVEF.^{13,18} Potential reasons for the slightly lower prevalence of subclinical pre-HF reported in the study by Russo and colleagues compared with HERZCHECK are manifold. For instance, Russo and colleagues used a more urban population from the Northern Manhattan Study, which could have affected the prevalence estimate, given that HF is generally known to be more common in structurally weak areas where access to specialists is low.^{1,2,18} A second reason that requires attention is that Russo and colleagues used echocardiography, whereas HERZCHECK utilized state-of-the-art CMR. While this and several other studies previously demonstrated that subclinical pre-HF can also be screened for using echocardiography, HERZCHECK deliberately used CMR due to its superior accuracy and reproducibility.^{18,19} Specifically, CMR offers the benefit of full myocardial coverage, allowing for strain analysis across all segments; higher spatial resolution with a better signal-to-noise ratio; and higher feasibility in obese patients with impaired acoustic conditions.^{16–18,20} In our trial, no participant was excluded due to morbid

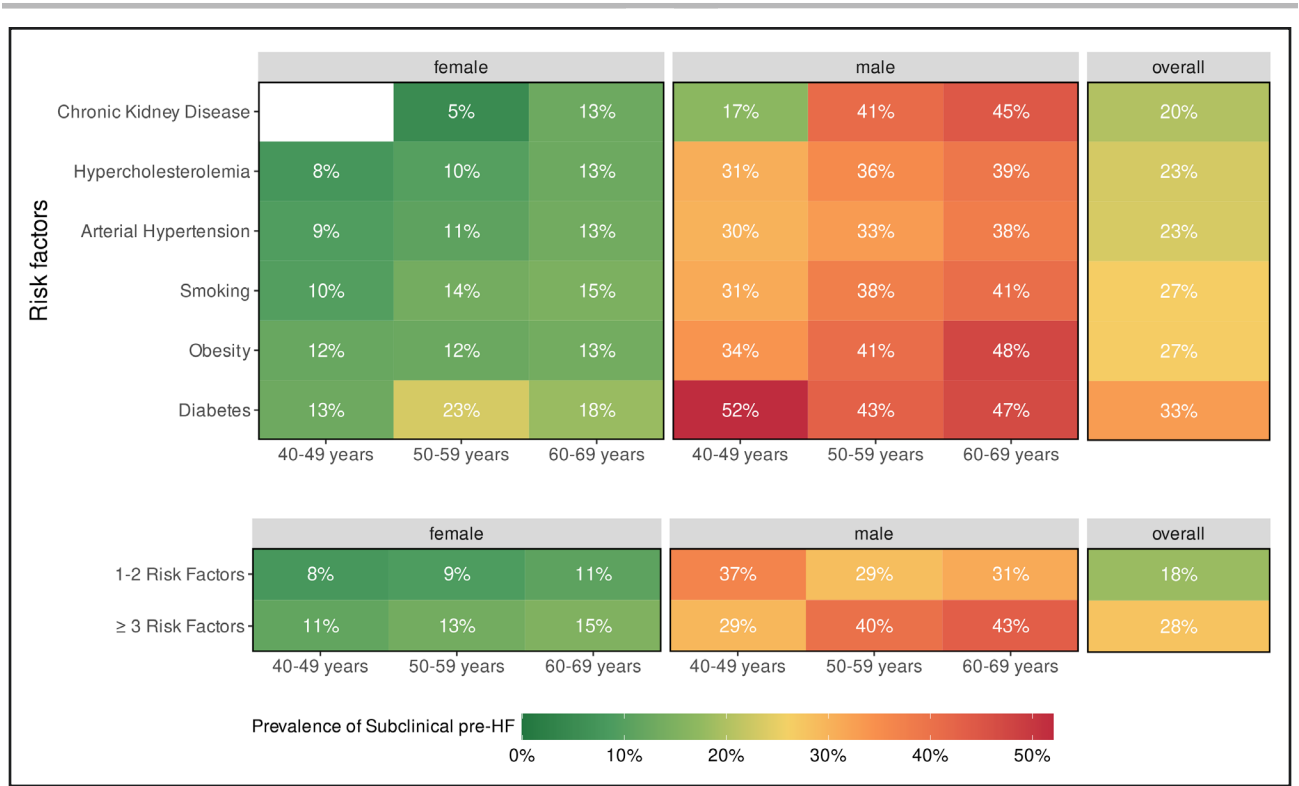


Figure 2. Prevalence of subclinical heart failure (HF) and risk factor constellations. Observed prevalence of subclinical pre-HF (ie, impaired global longitudinal strain) in different risk factor constellations.

obesity. The last factor, in particular, could be a reason why patients with impaired GLS could have been missed using echocardiography but were detected when using CMR. This is also supported by the fact that Russo and colleagues had to exclude 125 (15%) of the 854 participants included in their study due to insufficient image quality for speckle-tracking analysis.¹⁸ In our trial, only 12 (0.3%) of 4666 participants had to be excluded due to reduced image quality.

In addition, by comparison with an entropy-balanced control cohort, we demonstrate that our screening approach allows for the detection of HF $\approx$ 7 years earlier than traditional methods. This earlier detection provides a crucial opportunity to initiate preventive measures aimed at delaying or even preventing the progression to symptomatic HF. However, a significant challenge remains: there is currently no clear consensus on the optimal management of these patients. Current guidelines emphasize risk factor optimization, yet such optimization does not necessitate advanced imaging for the detection of subclinical pre-HF.¹³ Thus, while early identification of subclinical pre-HF offers a potential clinical advantage, it remains uncertain whether it translates into tangible benefits for patients in terms of long-term outcomes. Notably, data from other trials evaluating diagnostic imaging as a primary intervention indicate that it could—even in the absence of targeted therapies. For instance, the SCOT-HEART trial evaluating coronary computed tomography angiography in patients with stable chest pain previously

demonstrated that the knowledge of the presence of disease leads to better adherence to primary preventive measures and eventually improves clinical outcomes.²¹

Nevertheless, there is an urgent need for randomized controlled trials designed to evaluate which therapeutic interventions—be it lifestyle modifications (dietary adjustments, structured exercise programs), the use of wearable devices, or specific pharmacotherapy—can effectively delay or even prevent the progression to symptomatic HF. Specifically, it is crucial to determine whether all patients classified as having subclinical pre-HF should receive targeted therapy, or whether treatment should be reserved for specific subgroups—such as those with reduced GLS or other distinct criteria—to avoid overdiagnosis and overtreatment. Future research should also focus on refining risk stratification methods to better identify patients who are most likely to benefit from early intervention.

Other important aspects to consider when trying to assess the potential of the proposed screening algorithm to reduce the global burden of HF are its scalability in routine clinical care and its feasibility in different global settings. While both will ultimately need to be addressed in further studies, 2 specific features of the HERZ-CHECK screening are very promising in that regard. First, mobile CMR units can be deployed virtually anywhere in the world (high- and low-income countries), including the most remote areas, principally allowing for global adoption. Second, the GLS is a highly objective, quantifiable parameter that can be assessed (semi-) automatically.

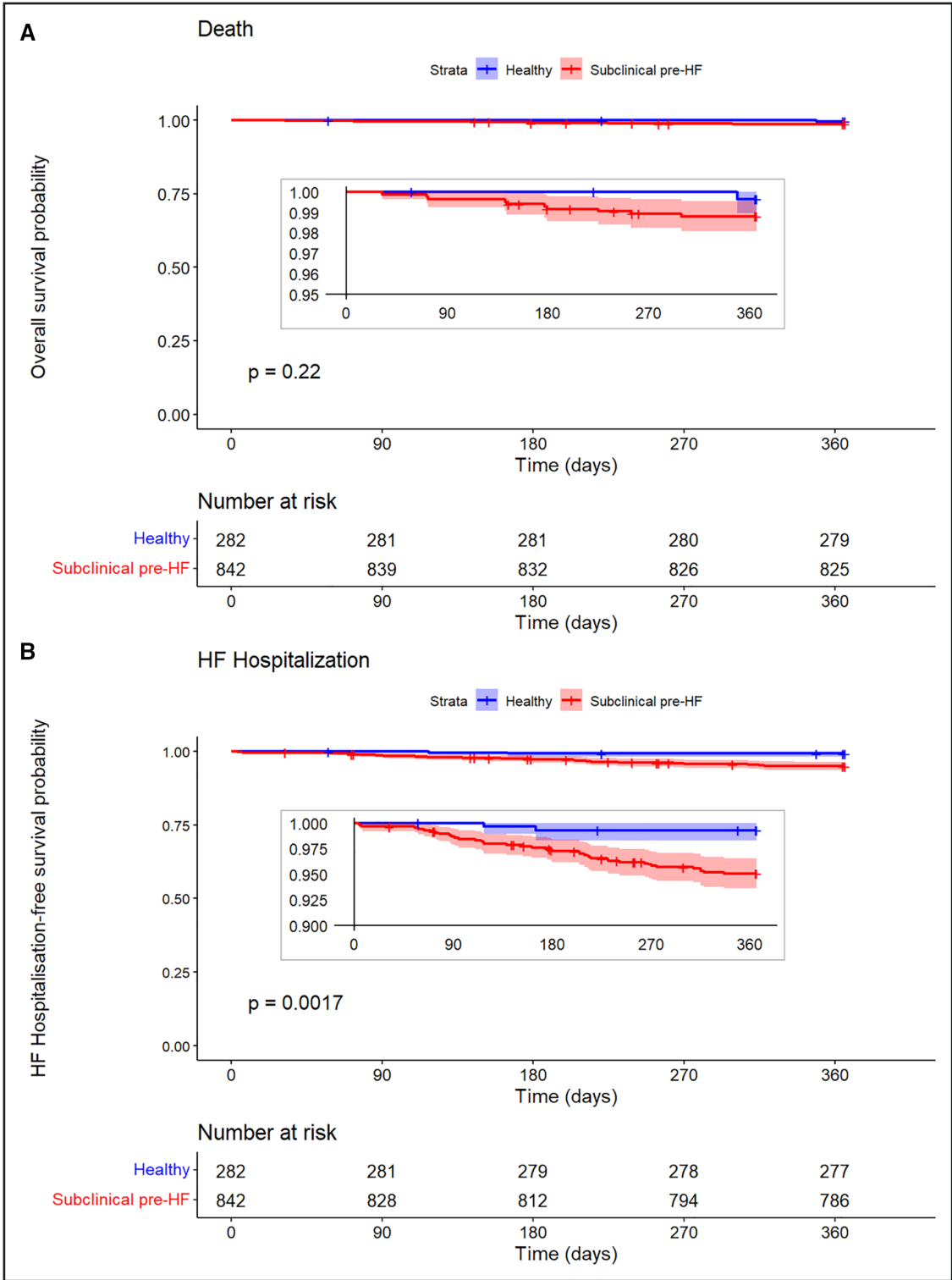


Figure 3. Kaplan-Meier-curves of HERZCHECK participants. Kaplan-Meier curves comparing time to (A) all-cause death and (B) first heart failure (HF) hospitalization between healthy participants (ie, preserved global longitudinal strain; blue lines) and those diagnosed with subclinical pre-HF (ie, impaired global longitudinal strain; red lines).

Therefore, expert interpretation is only required in cases of doubt and, as we demonstrated in this study, can then be provided via telemedicine. This will hopefully optimize the allocation and use of human resources by allowing highly trained experts to screen large numbers of individuals with excellent diagnostic accuracy. In addition, this approach might reduce the need for costly investments in smaller hospitals and help to set up networks with

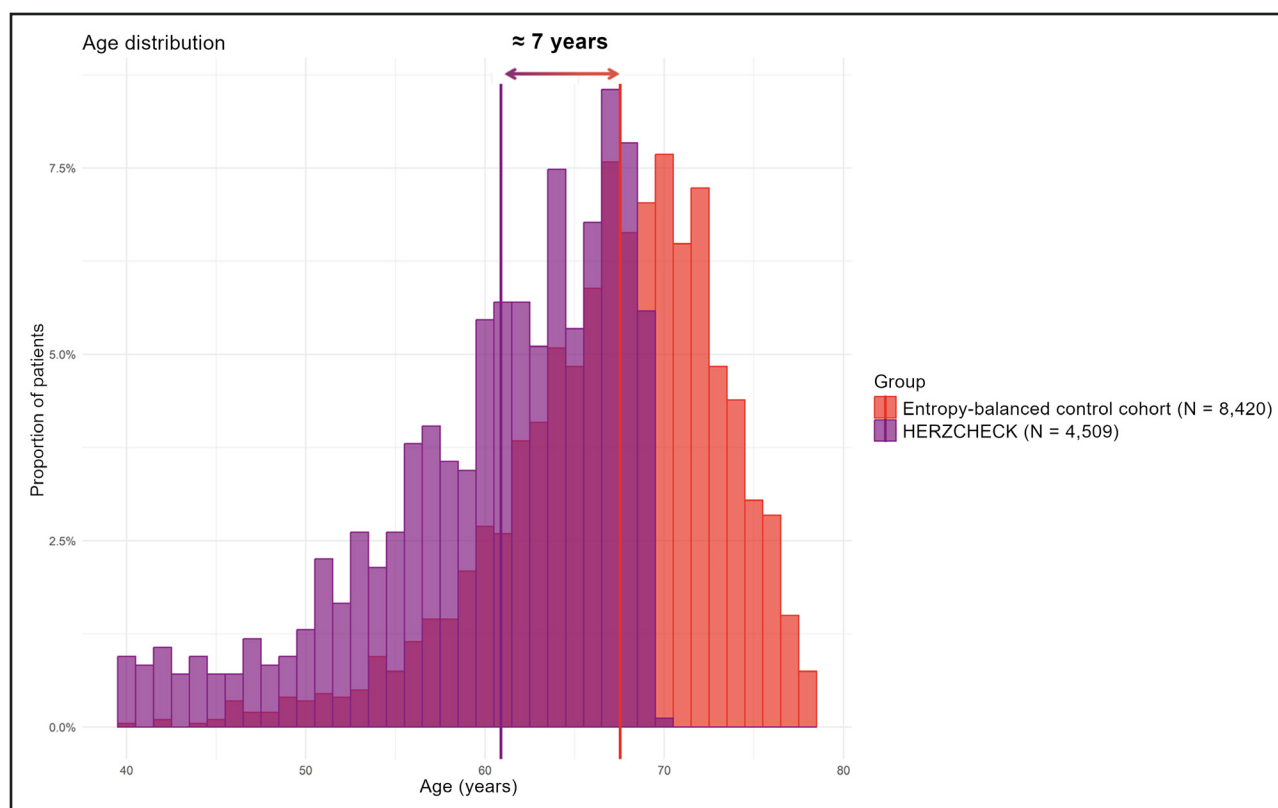


Figure 4. Time gained for prevention in participants with subclinical preheart failure (HF).

Overlapping histograms showing distribution of age at diagnosis of subclinical pre-HF (ie, impaired global longitudinal strain) in the HERZCHECK cohort (purple bars) and at first diagnosis of symptomatic HF in the entropy-balanced control cohort (red bars). Comparison of the weighted mean age at diagnosis (ie, 60.9 ± 7.0 years for subclinical pre-HF and 67.5 ± 6.4 years for symptomatic HF) demonstrates that the proposed screening yields ≈ 6.7 years of time gained for prevention of progression from subclinical pre-HF to symptomatic HF.

centralized expertise to provide broad access to high-end care at affordable costs for the healthcare system.

Limitations

HERZCHECK was focused on a population from rural and underresourced regions of Germany. It is therefore unclear whether the results can be transferred to urban populations. The CMR protocol did not contain the administration of contrast agents, which would have been necessary for the full diagnostic workup of cardiomyopathies. However, it is due in particular to the absence of contrast agents, that the proposed CMR protocol can be performed under telemedical supervision without a physician on site. This enables widespread application of the proposed screening algorithm, even in the most remote areas lacking trained healthcare staff and hardware. Another limitation is the primarily cross-sectional design, which precludes direct assessment of long-term HF risk in the entire cohort. This was partly addressed by analyzing 1-year health insurance claims data in a subcohort. In addition, complementary insight into the diagnostic lead time compared with the standard of care was obtained using a matched and entropy-balanced control cohort from claims data. Matching and entropy

balancing were performed without available information on the GLS and other clinical parameters, as these were not routinely reported in the claims data used for that purpose. However, due to the use of sophisticated statistical balancing methods including numerous covariates known to be associated with the cardiovascular risk, it can be assumed that the control cohort sufficiently matches the HERZCHECK subgroup considered for the respective analysis. Importantly, extended prospective follow-up studies allowing for definitive evaluation of the prognostic implications of CMR-based GLS are already planned. Furthermore, when using claims data, incident HF cases (CC) and adverse events may be misclassified. To account for such misclassification, different validation algorithms for incident HF were tested in sensitivity analyses presented in the [Supplemental Material](#). In addition, the definition of adverse events was applied to both participants with and without subclinical pre-HF (ie, not affecting the differences). Moreover, the observed association of male sex with elevated risk for subclinical pre-HF should be interpreted with caution, as it may reflect residual or unmeasured confounding, and further analyses will be required to clarify the underlying mechanisms. Last, several risk factors included in the presented regression analyses were self-reported

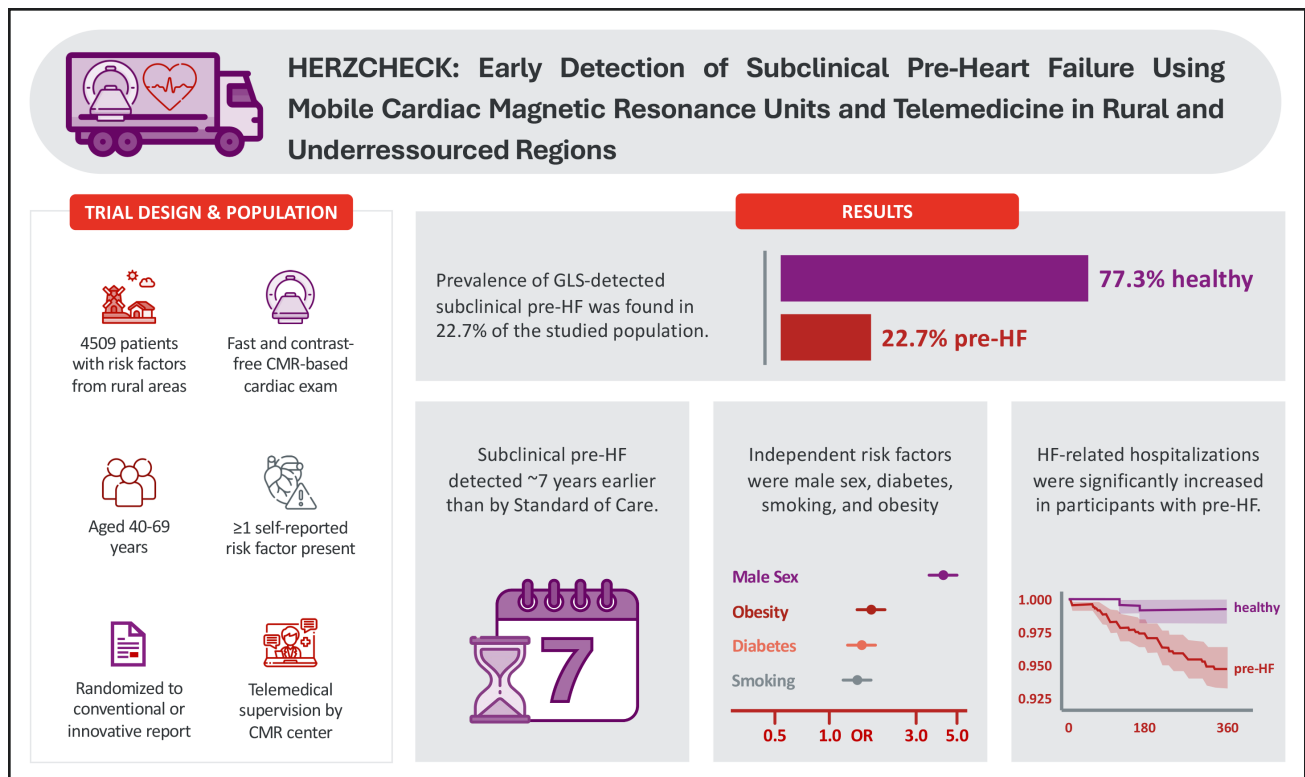


Figure 5. Illustration visualizing characteristics of the study design and population, as well as key study results. CMR indicates cardiac magnetic resonance; GLS, global longitudinal strain; HF, heart failure; and OR, odds ratio.

without an evaluation of more detailed information on their severity and treatment status, which may have influenced the ability to detect independent associations with subclinical pre-HF.

Conclusions

HERZCHECK provides a proposal for a contemporary, fully mobile, and telemedically supervised CMR-based screening approach for subclinical pre-HF that is tailored to the needs of the target population. This study shows that subclinical pre-HF affects approximately one fourth of the at-risk population in rural and under-resourced regions and that the proposed GLS-based CMR screening identifies patients suitable for preventive interventions ~7 years earlier than the current standard of care (Figure 5). In addition, HERZCHECK provides a sufficiently large database to distinguish cardiovascular risk factor constellations associated with particularly high risk for subclinical pre-HF. These constellations may help establish multiparametric definitions that will allow for even more specific selection of patients requiring improved patient care and could thus optimize the use of resources available to healthcare systems across the globe.

ARTICLE INFORMATION

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Author Contributions

Drs Kelle, Thiede, Steen, Remppis, Huppertz, Simic, Reber, Landmesser, Frey, Pieske, Nagel, Schmidt, Falk, and Friede conceived and designed the study. Drs

Kelle, Müller, Beyer, Thiede, Nolden, Tuit, Cvetkovic, Witt, and Reber collected the data. Drs Kelle, Müller, Beyer, Nolden, Wieditz, Tuit, Cvetkovic, Witt, Huppertz, Simic, Müller, Shukri, Stock, Kentenich, and Friede performed the analyses. Drs Kelle, Müller, Beyer, Wieditz, Kentenich, and Friede wrote the first draft of the manuscript. All authors critically reviewed the manuscript and provided intellectual input. All authors gave final approval for the publication of the manuscript.

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Disclosures

None.

Supplemental Material

Supplemental Methods S1–S5

Tables S1–S10

Figures S1–S6

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5.2 DP II: Health economic consequences of screening for pre-heart failure

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Cost-Effectiveness of a Global Longitudinal Strain-Based Screening and Prevention Program for Pre-Heart Failure Compared With Standard of Care

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Economic Evaluation

Cost-Effectiveness of a Global Longitudinal Strain-Based Screening and Prevention Program for Pre-Heart Failure Compared With Standard of Care

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ABSTRACT

Objectives: To prevent heart failure (HF), the global longitudinal strain (GLS) emerged as a promising systolic function parameter for targeted pre-HF screening and prevention measures. This analysis investigated the cost-effectiveness of a GLS-based screening and prevention program for pre-HF in a German at-risk population.

Methods: A patient-level simulation model was developed from the perspective of the German statutory health insurance. By comparing the lifetime costs and consequences of a GLS-based screening program with those of standard of care without screening, the incremental cost-effectiveness ratio (ICER) was calculated. Input parameters were obtained from HERZCHECK trial data and the literature. Results were presented as costs per quality-adjusted life-year (QALY) and costs per life-year (LY) gained. Deterministic and probabilistic sensitivity analyses examined the robustness of the results, and a model validation was performed. An option value was calculated to reflect the impact of the potential costs and benefits of future innovations.

Results: Compared with standard of care, the GLS-based screening program resulted in both additional costs (€7031) and benefits (0.10 QALYs/0.12 LY), with an ICER of €69 543/QALY and €59 552/LY. The probabilistic sensitivity analysis showed that the GLS-based screening program was cost-effective with a probability of 67% at a willingness-to-pay threshold of €100 000/QALY. While screening only men or patients aged ≥60 years decreased the ICER by 25% and 21%, respectively, considering the option value increased the ICER by 59%.

Conclusion: Our results indicate that a GLS-based screening program could be offered at an acceptable cost-effectiveness ratio. Specifying the target population may improve the cost-effectiveness.

Keywords: cost-effectiveness analysis, decision-analytic model, global longitudinal strain, micro-simulation, prevention, stage B heart failure.

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Highlights

- This economic evaluation using a patient-level simulation model provides first insights into the cost-effectiveness of a global longitudinal strain (GLS)-based screening and prevention program for pre-heart failure (HF) compared with the standard of care in Germany.
- A GLS-based screening and prevention program for pre-HF in a population at risk of HF enhances (quality-adjusted) life expectancy while resulting in additional costs compared with standard of care. The cost-effectiveness ratio is lower for men, individuals aged ≥60 years, and populations with higher pre-HF prevalence but increases when considering costs and benefits of future innovations.
- The GLS-based screening and prevention program for pre-HF may be offered at an acceptable cost-effectiveness ratio, particularly when specifying the target population. However, further evidence is needed to confirm the results.

Introduction

Heart failure (HF) is a global health problem that affected around 5% of the German population in 2023.¹ It is a progressive disease that is associated with a high mortality and morbidity,^{2,3} resulting in estimated costs of more than \$300 billion worldwide in 2017⁴ and €9.2 billion for the German healthcare system in 2023.⁵ This significant clinical and economic burden may be particularly reduced by identifying patients with (pre-symptomatic) pre-HF (American Heart Association [AHA]-classification stage B HF) and initiating preventive measures, such as risk factor modifications, lifestyle adaptations, and pharmacological therapy that can delay the patients' risk of deteriorating to (symptomatic) HF (stage C/D HF).⁶ Although HF prevention

has therefore been the recent focus in clinical guidelines,^{6,7} no standardized screening program has yet been established in clinical practice⁸ (ie, pre-HF often remains unrecognized).

Recently, the global longitudinal strain (GLS) was defined as a pre-HF criterion⁶ and emerged as a promising marker for targeted screening. It enables the detection of even subtle systolic dysfunction and seems to be a precise predictor of incident HF.^{9–12} Based on these favorable characteristics, the HERZCHECK trial evaluated a GLS-based screening and prevention program for pre-HF.¹³ Targeting a German at-risk population, the prevalence of pre-HF, the time gained for early prevention before developing HF, and the 12-month clinical effectiveness of preventive interventions in pre-HF were evaluated.¹³

To inform decisions on the implementation and reimbursement of a GLS-based screening program for HF prevention, additional information on the long-term clinical and economic consequences is required. This economic modeling study therefore assessed the lifetime cost-effectiveness of a GLS-based pre-HF screening and prevention program provided to an at-risk population compared with standard of care (SoC) (ie, no screening) in Germany.

Methods

A patient-level simulation model was developed to evaluate the cost-effectiveness of a GLS-based screening and prevention program compared with SoC over lifetime (70 years). To reflect short-term changes in risks, a 1-month cycle length was applied. While taking into account the upfront screening costs of all patients at risk, the model targets the course of pre-HF patients (ie, individuals without pre-HF were not followed afterward because they do not incur any further relevant costs or benefits) (Fig. 1). The analysis was performed from the perspective of the Statutory Health Insurance (SHI), which covers the costs of healthcare services for almost 90% of the German population¹⁴ (ie, payer perspective).

The health economic analysis plan is provided in Appendix 9. The analysis was reported according to the Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022, Appendix 8).¹⁵

Patient Population and Comparators

This analysis was associated with the HERZCHECK trial (2021–2024), a cross-sectional cohort study with an integrated randomized controlled trial (RCT) that investigated the potential of GLS-based early detection and management of pre-HF in a northeast German at-risk population.¹³ The trial included 4509 participants aged 40 to 69 years with at least 1 predefined risk factor (ie, diagnosis of diabetes mellitus/hypertension/obesity/chronic kidney disease or tobacco consumption). All participants underwent a mobile, telemedically supervised, stress- and contrast-agent-free cardiac magnetic resonance (CMR) with GLS measurement using semiautomatic feature tracking. Accordingly, pre-HF was defined using the a priori defined GLS cut-off ($\geq -15\%$), and participants were followed for 12 months.^{13,16}

Targeting the HERZCHECK screening population, for the economic model, 50 000 individuals with pre-HF were simulated by bootstrapping screen-detected HERZCHECK participants ($n = 1023$). They were on average 60 ± 7 years old, had a median GLS of -14.4% [interquartile range -15.0% to -13.3%], and were mostly male (72%, self-reported biological sex¹⁷). Further participants' characteristics are presented in Appendix 1.

In the screening arm of the model, as result of known pre-HF, these simulated individuals received lifestyle interventions (ie, exercise therapy and nutritional counseling as described in Appendix 4) to reduce the risk of becoming symptomatic or dying. In the SoC arm reflecting actual clinical practice in Germany without screening, HF was assumed to be diagnosed later, at the onset of symptoms. Consequently, pre-HF of the simulated individuals remained unrecognized, and no preventive interventions were provided.

Model Overview

To reflect the potential clinical course after the onset of pre-HF, the model comprised 4 health states: (1) (pre-symptomatic) pre-HF, at which all patients started; (2) (symptomatic) HF without HF hospitalization; (3) (symptomatic) HF with HF hospitalization; and (4) death. Possible transitions are presented in Figure 1. Per the AHA HF stages, patients could not return from HF to pre-HF.⁶

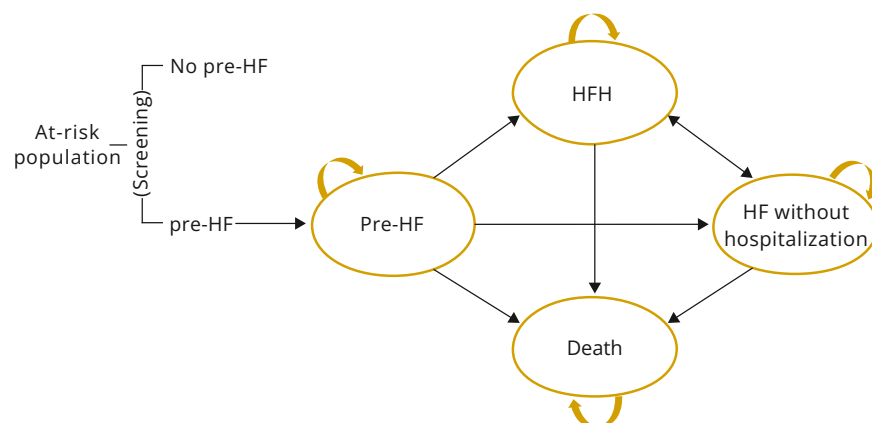
To reflect the chronic progressive nature of HF, short- and long-term implications of HF hospitalizations were incorporated into the model.¹⁸ In the short term, HF hospitalizations increase both the patients' mortality and the risk of HF rehospitalization.^{19–22} This was implemented using time-dependent transition probabilities based on trackers (time since last HF hospitalization). In the long term, mortality and the risk of HF rehospitalization increase with the number of HF hospitalizations.^{3,23–25} This was implemented using a hazard ratio (HR) per (tracked) HF hospitalization for mortality and HF rehospitalization, respectively.¹⁸

The model was constructed and analyzed using TreeAge Pro 2023 (TreeAge Software LLC).²⁶

Input Parameters

The model was parameterized based on (1) HERZCHECK trial data (patient records, standardized patient questionnaires, claims data from AOK Nordost), (2) German public statistics, and (3) published evidence. Published evidence was added because of a lack of long-term data in the HERZCHECK trial. Furthermore, the

Figure 1. Model structure.



HF indicates heart failure; HFH, heart failure hospitalization.

GLS-value used for outcome measurement in the trial is a surrogate parameter,¹³ requiring linkage to patient-relevant outcomes. Information on the search for and selection of adequate literature is provided in [Appendix 2](#). Input parameters are summarized in the following sections. For details, see [Appendix 2](#).

Transition probabilities

Monthly sex- and GLS-specific transition probabilities for pre-HF patients were calculated based on the baseline risks and HRs per 1%-change in GLS observed in a Danish cohort study.²⁷ The HF incidence was stratified into outpatient and inpatient diagnoses according to the proportions obtained from claims data of incident HF patients ($n = 2005$).¹⁶ Because of a lack of GLS-specific all-cause mortality data, sex- and GLS-specific cardiovascular mortality from the Danish cohort²⁷ was combined with sex- and age-specific non-cardiovascular (background) mortality from German death statistics 2023.²⁸

Transition probabilities for HF patients (with or without hospitalization) were obtained from 3 retrospective European cohort studies.^{25,29,30} For patients who have not yet been hospitalized, time-dependent transitions were based on incident HF patients diagnosed in the outpatient setting.²⁹

For patients in their first HF hospitalization, data on HF rehospitalizations and mortality³⁰ were fitted to a log-normal curve and a log-logistic curve in accordance with a previous model¹⁸ ([Appendix 2](#)). For the first year, time-dependent monthly probabilities were then derived from the proportion of subjects who were admitted to hospital or died at the end of a cycle (provided they were event-free at the start of the cycle).¹⁸ Thereafter, constant probabilities were assumed based on evidence for increased rehospitalization and mortality rates after a HF hospitalization that gradually decreased and stabilized after 1 year.^{18,19,22}

For patients with more than 1 HF hospitalization, monthly probabilities of HF rehospitalization and death were adjusted using mean HRs per additional HF hospitalization.²⁵

To adjust for an increase in mortality and HF incidence with age,^{31,32} age-dependent HRs were applied.^{28,33} All data were transformed using common equations.^{34,35}

Intervention effect

To determine the effect of preventive measures, HRs on mortality and HF incidence of pre-HF patients were obtained from a systematic review that included 94 moderate to high-quality RCTs on behavioral counseling interventions focusing on diet and physical activity.³⁶ The associated meta-analyses of homogeneous studies reported pooled effects on cardiovascular events (9 RCTs, $n = 12\,551$) and all-cause mortality (18 RCTs, $n = 17\,939$) that were applied on the progression to HF and death, respectively.³⁶ In line with some of the pooled RCTs,³⁶ a 12-month intervention period was assumed. According to the follow-up of the pooled RCTs (cardiovascular events: 1 to 16 years, mean: 6.6 years; all-cause mortality: 0.5 to 16 years, mean: 3.3 years),³⁶ the effect was conservatively modeled for 6 years, with a linear decrease after 3 years.

Utilities

For pre-HF, the utility was obtained using health-related quality-of-life data from the HERZCHECK trial. On this basis, using a published mapping algorithm for Germany,³⁷ the mean European Quality-of-Life 5-dimensions 5-level questionnaire (EQ-5D-5L) index value was estimated using asymptomatic participants' responses to the validated PROMIS-29 profile questionnaire³⁸ ([Appendix 3](#)).³⁹

The utility for HF without hospitalization was obtained from EQ-5D-5L values of prevalent HF patients from several European

countries.⁴⁰ For patients with HF hospitalization, a decrease based on EQ-5D values of an HF population from the United Kingdom⁴¹ was applied for the month of hospitalization and 2 months after discharge, respectively, as reported in a previous HF model.⁴¹

Resource use and costs

Per the study perspective, direct medical costs reimbursed by the SHI were included.^{42,43} Screening costs were obtained from the HERZCHECK trial, including the patients' telemedical education, the CMR and its administration, and the medical record. To reflect overall screening costs, costs per detected pre-HF patient (instead of costs per screened individual) were implemented by dividing the unit costs per screened individual by the pre-HF prevalence.

In line with the evidence used for the effect measure,³⁶ positively screened participants were assumed to receive a 12-month lifestyle intervention comprising several individual and group sessions for exercise therapy and nutritional counseling ([Appendix 4](#)). Corresponding costs were obtained from national fee schedules.^{44,45}

Pre-HF costs of positively screened patients were calculated as a mean difference in monthly outpatient and medication costs per HERZCHECK participant in the 12 months before and after the screening, using claims data.

Costs of the HF states including HF hospitalizations, outpatient visits, and medication were calculated based on claims data for incident HF patients ($n = 2005$) from 2014 to 2022.¹⁶ Furthermore, rehabilitation costs for patients aged ≥ 67 years (which are covered by the SHI^{46,47}) were based on 2710 individuals with chronic HF obtained from the German Competence Network Heart Failure.^{48,49}

All costs were expressed in euros and adjusted to 2023 euros using the German consumer price inflation (via R, package "priceR"⁵⁰).^{35,43} Cost calculations from claims data were conducted with R (version 4.4.1 or higher), R Foundation for Statistical Computing.⁵¹

Model Output

Based on lifetime costs and effects of the GLS-based screening program and SoC, the incremental cost-effectiveness ratio (ICER)⁵² was calculated as cost per quality-adjusted life-year (QALY) gained and cost per life-year (LY) gained.

Costs and effects were discounted at a 3% annual rate,⁴³ and half-cycle correction was applied.⁵³

Subgroup analyses were conducted to evaluate whether results differ according to patients' sex (male/female) and age at screening (40-59/ ≥ 60 years).

Sensitivity Analyses

To identify the parameters with the largest impact on the results, deterministic sensitivity analyses were run for all input parameters,⁵⁴ applying the ranges presented in [Appendix 2](#). Additionally, structural sensitivity analyses were performed to assess the impact of including costs of additional LYs⁴³ and applying the general population HF incidence and mortality for patients aged ≥ 90 years (instead of a continuous age-dependency via HRs). Furthermore, scenario analyses were performed to evaluate the impact of varying pre-HF prevalence (15%/50%) and effect duration (2/10 years).

Applying appropriate distributions ([Tables 1 and 2](#)),⁵⁵ a probabilistic sensitivity analysis (PSA) with 1000 iterations was conducted to model a simultaneous change of all input parameters except the discount rate.⁵⁴ A cost-effectiveness acceptability curve was estimated to show the probability of SoC and the GLS-

Table 1. Clinical input parameters.

Parameter	Value	Distribution*	Source
pre-HF prevalence	0.2268	Beta ($\alpha = 1023$, $\beta = 3486$)	Kelle et al ¹⁶
Mortality (probability per month)			
Background mortality (pre-HF women)	40-<45y: 6.0165E-05, 45-<50y: 9.6579E-05, 50-<55y: 1.5990E-04, 55-<60y: 2.5747E-04, 60-<65y: 4.2791E-04, 65-<70y: 6.8235E-04, 70-<75y: 1.0196E-03, 75-<80y: 1.6174E-03, 80-<85y: 2.6684E-03, 85-<90y: 4.7333E-03, $\geq 90y$: 1.0102E-02	PERT (mode [†] , 95% CI)	Gesundheitsberichterstattung des Bundes ²⁸
Background mortality (pre-HF men)	40-<45y: 1.0808E-04, 45-<50y: 1.6015E-04, 50-<55y: 2.6463E-04, 55-<60y: 4.2941E-04, 60-<65y: 7.2657E-04, 65-<70y: 1.1421E-03, 70-<75y: 1.6919E-03, 75-<80y: 2.5359E-03, 80-<85y: 4.0068E-03, 85-<90y: 6.5370E-03, $\geq 90y$: 1.2314E-02	PERT (mode [†] , 95% CI)	Gesundheitsberichterstattung des Bundes ²⁸
CV mortality (pre-HF women) GLS = -11.8% HR per 1% GLS increase	0.0006 1.03	PERT (mode [†] , 95% CI)	Biering-Sørensen et al ²⁷
CV mortality (pre-HF men) GLS = -11.8% HR per 1% GLS increase	0.0007 1.11	PERT (mode [†] , 95% CI)	Biering-Sørensen et al ²⁷
Age-dependent CV mortality (pre-HF): HR per 5-year age class	Women: 1.60, Men: 1.57	PERT (mode [†] , $\pm 10\%$)	Gesundheitsberichterstattung des Bundes ²⁸
All-cause mortality without previous HFH (symptomatic HF)	Month of diagnosis: 0.0700; 1 month - 11 months after diagnosis: 0.0118; ≥ 12 months after diagnosis: 0.0100	PERT (mode [†] , 95% CI)	Lawson et al ²⁹
All-cause mortality with 1 HFH (symptomatic HF)	Month of HFH: 0.1319; 1 month after HFH: 0.0405; 11 months after HFH: 0.0100; ≥ 12 months after HFH: 0.0075	PERT (mode [†] , 95% CI)	Corrao et al ³⁰ , log-logistic curve
Progression: HR per HFH (symptomatic HF)	1.33	lognormal (mean of log = 0.2883, SD of log = 0.0137)	Lindmark et al ²⁵
Age-dependent mortality (symptomatic HF): HR per 5-year age class	Women: 1.38; Men: 1.44	PERT (mode [†] , $\pm 10\%$)	Assumption based on Gesundheitsberichterstattung des Bundes ²⁸
HF incidence (probability per month)			
GLS = -11.8%	Women: 0.0007; Men: 0.0014	PERT (mode [†] , 95% CI)	Biering-Sørensen et al ²⁷
HR per 1% GLS increase	Women: 1.09; Men: 1.22		Biering-Sørensen et al ²⁷
Age-dependent incidence: HR per 5-year age class	1.05	PERT (mode [†] , $\pm 10\%$)	Assumption based on Drozd et al ³³
Proportion of inpatient diagnoses HFH (probability per month)	0.5980	Beta ($\alpha = 1,199$, $\beta = 806$)	HERZ-CHECK
1. hospitalization (symptomatic HF)	<12 months after diagnosis: 0.0102; ≥ 12 months after diagnosis: 0.0054	PERT (mode [†] , 95% CI)	Lawson et al ²⁹
Rehospitalization after 1 HFH (symptomatic HF)	Month of HFH: 0.0418; 11 months after HFH: 0.0084; ≥ 12 months after HFH: 0.0066	PERT (mode [†] , 95% CI)	Corrao et al ³⁰ , lognormal curve
HR per HFH (symptomatic HF)	1.25	lognormal (mean of log = 0.2192, SD of log = 0.0087)	Lindmark et al ²⁵
Intervention effect			
HR incidence of HF (screening arm)	0.80	lognormal (mean of log = -0.2231, SD of log = 0.0448)	O'Connor et al ³⁶
HR mortality (screening arm)	0.89	lognormal (mean of log = -0.1165, SD of log = 0.1140)	O'Connor et al ³⁶

CI indicates confidence interval; CV, cardiovascular; GLS, global longitudinal strain; HF, heart failure; HFH, heart failure hospitalization; HR, hazard ratio; SD, standard deviation; y, years.

*For probabilistic sensitivity analysis.

[†]The reported mean value was used as a proxy for the mode of the PERT distribution.

Table 2. Costs and utilities.

Parameter	Value	Distribution* (parameter)	Source
Costs (€/month per patient)			
One-time screening per screened individual [†] (screening arm)	672.00	PERT (mode [‡] , min = 482.00, max = 712.00)	HERZCHECK
Intervention (screening arm)	33.31	Gamma (mean, SD = 3.40)	GKV-Spitzenverband ^{44,45}
pre-HF (screening arm)	24.05	PERT (mode [‡] , min = 0.00, max = 73.50)	HERZCHECK
HF without hospitalization	without rehabilitation (age <67 years): 57.86; with rehabilitation (age ≥ 67 years): 88.77	Gamma (mean, SD = 2.46/2.83)	HERZCHECK, Biermann et al, and Krauth et al ^{48,49}
HFH [§]	8,778.58	Gamma (mean, SD = 316.15)	HERZCHECK
Utilities			
pre-HF	0.813	Beta (mean, SD = 0.007)	HERZCHECK, Klapproth et al ³⁷
HF without hospitalization	0.730	Beta (mean, SD = 0.008)	Fonseca et al ⁴⁰
Disutility of HFH	≤30 days after HFH: 0.105; 30-90 days after HFH: 0.054	Beta (mean, SD = 0.006/0.004)	McMurray et al ⁴¹

CI indicates confidence interval; CV, cardiovascular; GLS, global longitudinal strain; HF, heart failure; HFH, heart failure hospitalization; HR, hazard ratio; SD, standard deviation.

*For probabilistic sensitivity analysis.

[†]Costs per detected pre-HF patient were implemented in the model as costs per screened individual/pre-HF prevalence to evaluate parameter uncertainty of both parameters.

[‡]The reported mean value was used as a proxy for the mode of the PERT distribution.

[§]Cardiovascular main diagnosis with heart failure as main or secondary diagnosis.

based screening program being cost-effective according to the decision makers' willingness to pay (WTP).

Model Validation

To confirm the validity of the model, face validation, external validation, and cross-validation were applied, and technical accuracy was ensured.^{56,57} Details were reported according to the "Assessment of the Validation Status of Health Economic decision models" checklist⁵⁷ (Appendix 7).

Option Value

To take into account the patients' opportunity to benefit from future innovations during their extended life (option value [OV]) and the economic consequences of these innovations, the model was extended. Logarithmic trends were applied to the HF incidence and mortality, and an exponential trend was applied to costs (Appendix 2). The incremental OV was ultimately estimated as the differences in incremental QALYs and LYs between the basic model and the OV model. In addition, changes in incremental costs and ICERs between the models were calculated.^{58,59}

Results

The key input parameters are presented in Tables 1 and 2. See Appendix 2 for details.

Base-Case and Subgroup Analyses

Compared with SoC (no screening), the GLS-based screening and prevention program was associated with additional benefits of 0.10 QALYs and 0.12 LYs, and additional costs of €7031. This resulted in an ICER of €69 543/QALY and €59 552/LY, respectively.

Subgroup analyses revealed a lower ICER for men than women (€52 379/QALY vs €116 394/QALY) and for patients aged ≥60

years than for those aged 40 to 59 years (€54 842/QALY vs €97 086/QALY). See Table 3 for detailed results.

Sensitivity Analyses

The results of the deterministic sensitivity analyses are presented in Figure 2. The parameters with the largest impact on the results were the costs of pre-HF, the HF incidence, the discount rate, the intervention effect on HF incidence, the mortality of pre-HF patients, and the screening costs (in that order).

The structural sensitivity analysis including costs of additional LYs increased the ICER by 21% (€84 165/QALY) compared with the base case. In contrast, applying the general population risk at age ≥90 years led to a 23% reduced ICER (€53 434/QALY).

Scenario analyses with a higher pre-HF prevalence of 50% and a longer effect duration of 10 years resulted in a decrease of the ICER by 23% (€53 541/QALY) and 38% (€43 390/QALY), respectively, compared with the base case. See Table 3 for detailed results on sensitivity and scenario analyses.

The 1000 iterations of the PSA spread across the upper quadrants of the cost-effectiveness plane (Fig. 3). 81.5% of the iterations (upper-right quadrant) showed additional benefits and costs of the GLS-based screening program compared with SoC. However, in 18.5% of the iterations (upper-left quadrant), the GLS-based screening program was dominated by SoC because of additional costs and less benefit. As shown in the cost-effectiveness acceptability curve (Appendix 5), the probability of the GLS-based screening program being cost-effective was 29% at a WTP of €30 000/QALY and increased to 67% at a WTP of €100 000/QALY.

Model Validation

The external validation showed that the results were in line with published data. For example, the mean age at symptom onset in this model was comparable to that reported in a German

Table 3. Results.

	Costs (€)	Incremental costs (€)	Effectiveness		Incremental effectiveness		ICER	
			QALY	LY	QALY	LY	€/QALY	€/LY
Base case								
SoC	2362.56		11.18	13.89				
Screening	9393.97	7031.41	11.28	14.01	0.1	0.12	69 542.87	59 551.58
Subgroup: Men								
SoC	2651.54		10.97	13.64				
Screening	8440.17	5788.63	11.08	13.77	0.11	0.13	52 378.79	44 990.45
Subgroup: Women								
SoC	1797.70		11.76	14.58				
Screening	11 946.91	10 149.21	11.85	14.69	0.09	0.10	116 393.60	98 552.89
Subgroup: Age 40-59 years								
SoC	2992.09		13.47	16.74				
Screening	11 104.64	8112.55	13.55	16.84	0.08	0.10	97 085.75	84 917.81
Subgroup: Age ≥ 60 years								
SoC	2051.60		9.79	12.16				
Screening	8413.45	6361.85	9.91	12.30	0.12	0.14	54 842.30	46 223.95
Sensitivity analysis: Cost of additional LY								
SoC	145 973.06		11.18	13.89				
Screening	154 482.91	8509.85	11.28	14.01	0.10	0.12	84 165.04	72 072.97
Sensitivity analysis: No age-dependent HR								
SoC	2190.57		11.82	14.66				
Screening	9537.26	7346.69	11.96	14.83	0.14	0.17	53 433.74	44 465.85
Scenario analysis: Prevalence 15%								
SoC	2362.56		11.18	13.89				
Screening	10 912.05	8549.49	11.28	14.01	0.10	0.12	84 557.12	72 408.71
Scenario analysis: Prevalence 50%								
SoC	2362.56		11.18	13.89				
Screening	7776.05	5413.49	11.28	14.01	0.10	0.12	53 541.10	45 848.80
Scenario analysis: Effect duration 2 years								
SoC	2362.56		11.18	13.89				
Screening	9438.49	7075.94	11.22	13.94	0.04	0.04	189 520.21	163 024.45
Scenario analysis: Effect duration 10 years								
SoC	2362.56		11.18	13.89				
Screening	9359.93	6997.37	11.34	14.08	0.16	0.12	43 390.05	36 914.73
HR indicates hazard ratio; ICER, incremental cost-effectiveness ratio; LY, life-year; QALY, quality-adjusted life-year; SoC, standard of care.								

HR indicates hazard ratio; ICER, incremental cost-effectiveness ratio; LY, life-year; QALY, quality-adjusted life-year; SoC, standard of care.

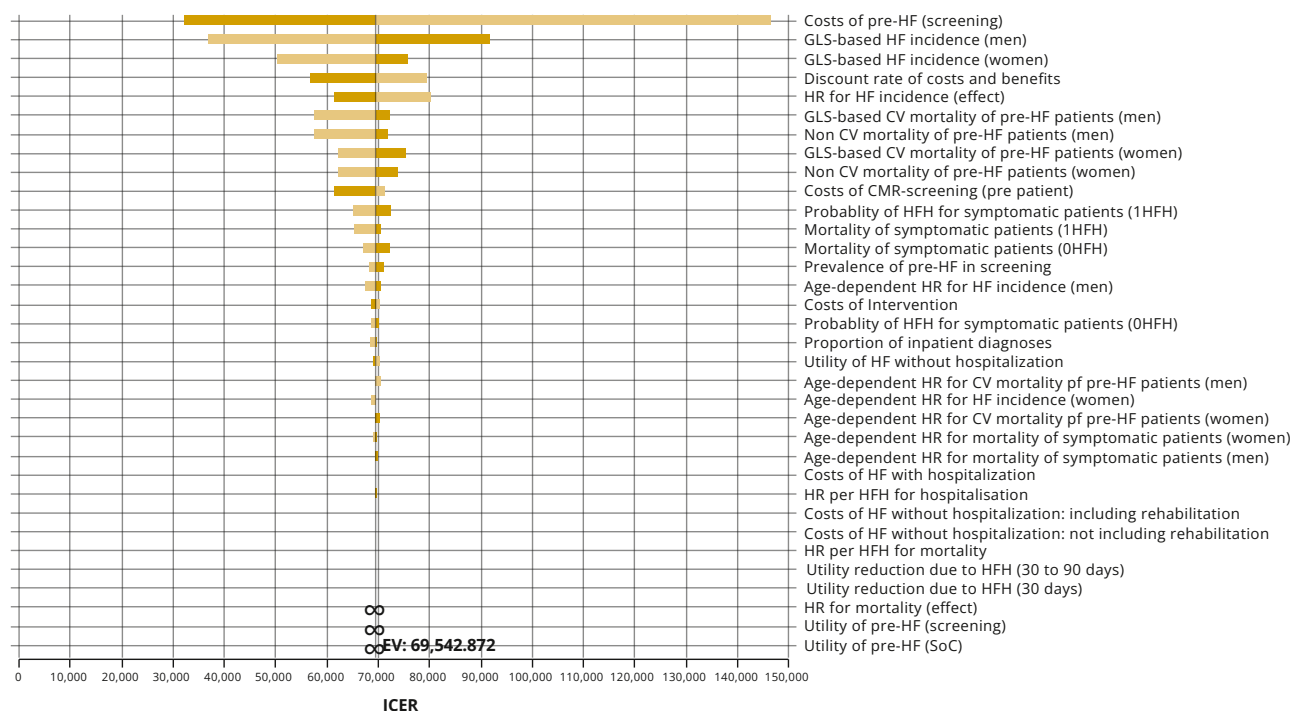
claims data analysis (72 vs 73 years).⁶⁰ Furthermore, the median survival of about 5 years for HF patients in this model was consistent with a reported pooled 5-year survival of 56%.³² In contrast, the 9-year HF incidence in this model, based on the Danish study used for parametrization,²⁷ was lower than that observed in a historical control group (CG) in the HERZCHECK trial (9% vs 26%).¹⁶ This might be explained by a higher prevalence of risk factors for HF (eg, male sex, hypertension, and diabetes⁶) in the CG compared with the Danish study population or by differences in the GLS distribution, which was not available for the CG.^{16,27}

For cross-validation, no health economic model evaluating the cost-effectiveness of a GLS-based pre-HF screening compared

with SoC was identified. One model comparing a GLS-based with a left ventricular ejection fraction (LVEF)-based strategy for HF diagnosis resulted in dominance of the GLS-based strategy (ie, lower costs and additional benefit). The result's deviation from this model might be explained by differences in the comparator (LVEF assessment vs no screening in this model), the target population (patients with risk factors and prevalent HF vs only patients with risk factors), the setting (United States vs Germany), and the type and effect of the intervention (medication reducing HF hospitalizations vs lifestyle intervention reducing HF incidence and mortality).⁶¹

Extreme value testing with a 0 effect and 0 costs for screening, intervention, and pre-HF resulted in the same costs and benefits for

Figure 2. Tornado diagram from deterministic sensitivity analyses. Tornado diagram presenting the impact of input parameters on the ICER (light: ICER for a higher value of the input parameter, dark: ICER for a lower value of the input parameter). For ranges of variation see [Appendix 2](#).



CMR indicates cardiac magnetic resonance; CV, cardiovascular; GLS, global longitudinal strain; HF, heart failure; HFH, heart failure hospitalization; HR, hazard ratio; SoC, standard of care.

the GLS-based screening and SoC, supporting the model's technical accuracy. See [Appendix 7](#) for details on the model validation.

However, the incremental costs increased by 59% to €11 189, resulting in an ICER of €110 854/QALY.

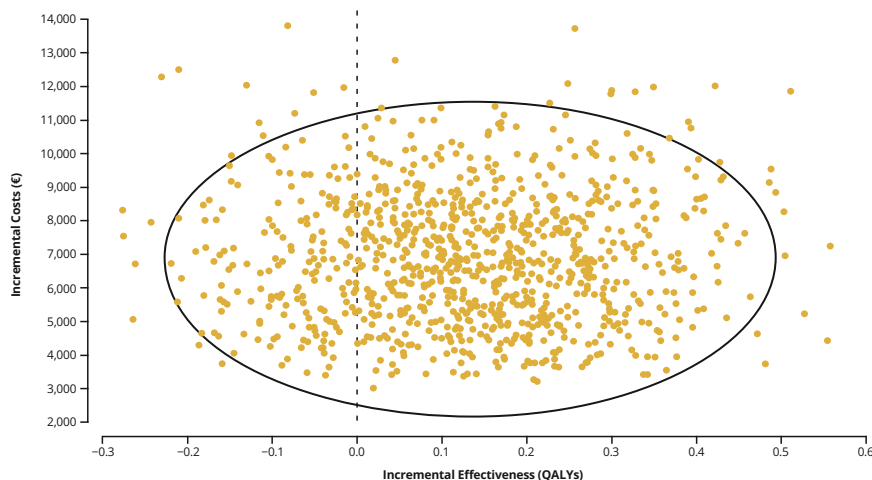
Option Value

The results of the OV scenario are presented in [Appendix 6](#). In the OV scenario, the incremental QALYs and LYs did not change.

Discussion

In comparison with SoC, the GLS-based screening program for early identification and management of pre-HF is likely to

Figure 3. Scatterplot from PSA (GLS-based screening vs. SoC). Scatterplot presenting the results for incremental costs and benefits of the GLS-based screening compared with SoC of the 1000 iterations in PSA (with 95% confidence ellipse).



GLS indicates global longitudinal strain; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year; SoC, standard of care.

result in both additional benefits (QALYs, LYs) and costs (leading to an ICER of almost €70 000/QALY). This was confirmed by sensitivity analyses and was consistent across subgroups by age and sex. The ICER decreased when targeting the analysis at men, patients aged ≥ 60 years, or patients with known risk factors associated with a higher pre-HF prevalence and HF incidence. However, taking medical advancement into account, no incremental OV in benefits was observed, but incremental costs increased considerably, resulting in an increased ICER.

The results indicate that long-term savings due to a delay or prevention of the progression to HF do not outweigh the initial costs of the GLS-based screening program. There are 2 main reasons for this result: first, only about 20% of pre-HF patients in the model were later diagnosed with HF, resulting in a low number of HF cases being prevented or delayed. To improve cost-effectiveness, patients at higher risk of progression to HF (ie, higher HF incidence) need to be targeted (Fig. 2). Additional pre-HF criteria (eg, increased level of B-type natriuretic peptide [BNP] or filling pressure⁶) or risk factors associated with HF (eg, diabetes mellitus, obesity^{2,6}) could therefore be considered besides the GLS.

Second, compared with SoC, the initial costs of screening and those of treatment in the pre-HF state impede a more favorable cost-effectiveness ratio. Because of the pre-HF prevalence of 23% in our target population,¹⁶ more than 4 individuals need to be screened to detect 1 case, resulting in high costs per detected pre-HF patient. Limiting the CMR-screening to those with a higher probability of detrimental GLS (ie, with strong predictors such as smoking or obesity¹⁶) would reduce screening costs and improve cost-effectiveness (Fig. 2, Table 3). Alternatively, pre-selecting patients using less expensive methods (eg, echocardiography) could reduce the number of patients receiving CMR.

The aforementioned factors may also explain the differences observed in subgroup analyses. For example, compared with the base case, a 25% and 21% reduced ICER was obtained in men and patients aged ≥ 60 years who have a higher pre-HF prevalence and HF incidence.^{16,27}

The lack of an incremental OV in benefits can be explained by the fact that the intervention effect was implemented using an HR, and the same trend was applied in the screening and SoC arm. The OV thus increased the absolute benefits in both arms, but the relative ratio remained unchanged. A stronger trend in the screening arm due to improved detection of pre-HF would result in an incremental OV. The higher incremental costs in the OV model resulted from the increasing trend applied to the accumulating pre-HF costs for positively screened patients.

In recent decades, the growing HF prevalence and a more profound understanding of predictors of HF have increased awareness of HF screening and prevention. However, screening is not yet established in clinical practice,⁸ which might reflect some uncertainty regarding clinical benefits and cost-effectiveness. As a widely used marker of left ventricular dysfunction and a crucial parameter in HF management,^{6,62} the LVEF may be used for screening. However, in pre-HF, structural cardiac damage might occur even when the LVEF is normal.⁶² One feasible approach for identifying patients with pre-HF are biomarkers.⁶³ In particular, BNP-based screening may reduce the combined rates of left ventricular dysfunction and HF and be cost-effective^{64,65} and is therefore recommended for patients at risk of HF in the AHA clinical practice guidelines.⁶ However, some cardiac imaging parameters permit the assessment of early structural or functional cardiac damage.⁶⁶ In particular, the GLS enables the detection of even subtle cardiac damage and has emerged as

precise predictor of HF.^{9–12} In the HERZCHECK trial, a GLS-based screening program was shown to be feasible and to detect pre-HF several years before HF would have been diagnosed in SoC.¹⁶

Other long-term health economic evaluations on screening programs for asymptomatic cardiac dysfunctions (reduced LVEF, elevated BNP level) also resulted in additional costs and benefits of the screening compared with SoC.^{64,67,68} Over lifetime, an ICER of ~€44 000/QALY (adjusted to 2023 euros) was reported for a screening based on a novel artificial intelligence electrocardiogram with subsequent medical therapy in patients aged 65 years.⁶⁸ This is comparable to the results for our subgroup of patients aged ≥ 60 years (€46 224/QALY). Furthermore, ICERs of ~€38 000/QALY and ~€130 000/QALY (adjusted to 2023 euros) were reported for BNP testing + echocardiography with subsequent medical therapy in men and women aged 60 years, respectively.⁶⁷ This supports the more favorable results of the GLS-based screening program in men compared with women in our analysis (€52 379/QALY vs €116 394/QALY). The difference to 1 study adopting the aforementioned model on artificial intelligence electrocardiogram screening, which reported cost savings compared with SoC, might result from higher screening and intervention costs and different settings.⁶⁹

In Germany, there is no common WTP threshold for assessing the cost-effectiveness of healthcare services. According to a cost-effectiveness threshold based on an increase in life expectancy and health expenditures of 1.01 gross domestic product per capita,⁷⁰ ie, €50 020/QALY in 2023 (gross domestic product of €49 525⁷¹), the GLS-based screening program would not be cost-effective. However, the highly innovative screening approach entailed some limitations in data availability, emphasizing the need to increase the robustness and interpretability of the results through prospective studies. In particular, further research should investigate long-term effects of GLS-based screening and prevention in pre-HF patients on patient-relevant outcomes. In addition, the costs of treatment for the pre-HF-state should be estimated by using a direct comparison to non-pre-HF patients. Furthermore, investigation on how to specify the target population with patients at higher risk of detrimental GLS and progression to HF is also required.

Strengths and Limitations

To the best of our knowledge, this is the first study evaluating the long-term clinical and economic consequences of a GLS-based screening and prevention program for pre-HF in an at-risk population compared with SoC. It addresses the increasing need for a structured screening and prevention program to reduce the clinical and economic burden of HF. Moreover, the validation of the combined trial and model-based approach followed recommended guidance⁵⁷ (Appendix 7). Intensive consultation with clinical experts also ensured appropriate model parametrization, and claims data used for cost calculations were highly complete and consistent.

Some limitations should be considered when interpreting the results. First, the model could not directly rely on a long-term clinical effect of a GLS-based screening and prevention program from HERZCHECK trial data. However, because pre-HF management currently focuses on risk factor control and lifestyle adaptations,⁶ a corresponding intervention effect was obtained from a large systematic review of RCTs on behavioral counseling interventions.³⁶

Second, only HF-related costs were included. This might result in an underestimation of cost-effectiveness because lifestyle interventions can also affect cardiovascular risk in general and noncardiovascular diseases, such as diabetes.^{36,72,73}

Third, the applicability of some clinical parameters to the model context may be disputable because they were obtained from European countries other than Germany^{25,27,29,30} with different epidemiology and healthcare resources.⁷⁴

Fourth, the GLS-based HF incidence was obtained from the Danish general population²⁷ (ie, no at-risk population), entailing the risk of underestimation of HF cases prevented or delayed (Appendix 7).

Finally, the generalizability of input parameters from the HERZCHECK trial might be limited because the trial focused on structurally weak regions (with higher HF prevalence and lower number of cardiologists^{75,76}) in north-east Germany,¹³ and claims data were only available from 1 insurance company¹³ that may cover a population with above-average morbidity.⁷⁷

Conclusion

Overall, for patients at risk of HF, the GLS-based screening program for early detection and management of pre-HF appears to be a promising approach, associated with gains in QALYs and LYs but also with additional costs compared with SoC. Because of uncertainty and variability in some key input parameters, further evidence is needed to confirm the results. In particular, evidence on the long-term effects of preventive interventions in pre-HF could increase the robustness of the results, and specifying the target population might improve the cost-effectiveness of the program.

Author Disclosures

Author disclosure forms can be accessed below in the [Supplemental Material](#) section.

Supplemental Material

Supplementary data associated with this article can be found in the online version at <https://doi.org/10.1016/j.jval.2026.04.002>.

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5.3 DP III: Sex differences in guideline adherence for suspected coronary artery disease

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Sex differences in guideline adherence for coronary angiography in patients with suspected chronic coronary syndrome in Germany: insights from the ENLIGHT-KHK trial

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Abstract

Background For the management of acute coronary syndrome, literature shows lower healthcare providers' guideline adherence for women than for men. Since less is known about the management of chronic coronary syndrome (CCS), this study investigated patient-related sex differences in providers' guideline adherence for invasive coronary angiography (CA) performed in patients with suspected CCS.

Methods Using data from the German ENLIGHT-KHK trial, patients with suspected CCS who underwent a CA were analysed. To assess the association between patient sex and physicians' adherence to the German National Disease Management Guideline "Chronic coronary artery disease" of 2019, binary logistic regression models were developed. Covariates included age, symptoms, risk factors, comorbidities, and non-invasive testing and its results. To examine sex differences in predictors of guideline adherence, models were run separately for women and men.

Results Two hundred seventy-three women and three hundred eighty-six men were included (aged 67 ± 10 years). Physicians' guideline adherence for CA was lower for women than for men (19.4% vs. 30.1%, $p = 0.002$). CAs were less likely to be guideline-adherent for women with suspected CCS than men (OR 0.4, $p < 0.05$). Guideline adherence predictors differed between women and men. For example, men's predictors included non-invasive testing and its results, age, typical angina and smoking; of these, only a positive non-invasive test result had an impact for women.

Conclusion Our results indicate a less guideline-adherent diagnostic workup of CA for women with suspected CCS than men. This might reflect a limited awareness of CCS in women and insufficiently sex-specific guideline recommendations.

Trial registration German Clinical Trials Register DRKS00015638, Registered February 19, 2019; Universal Trial Number (UTN): U1111-1227-8055.

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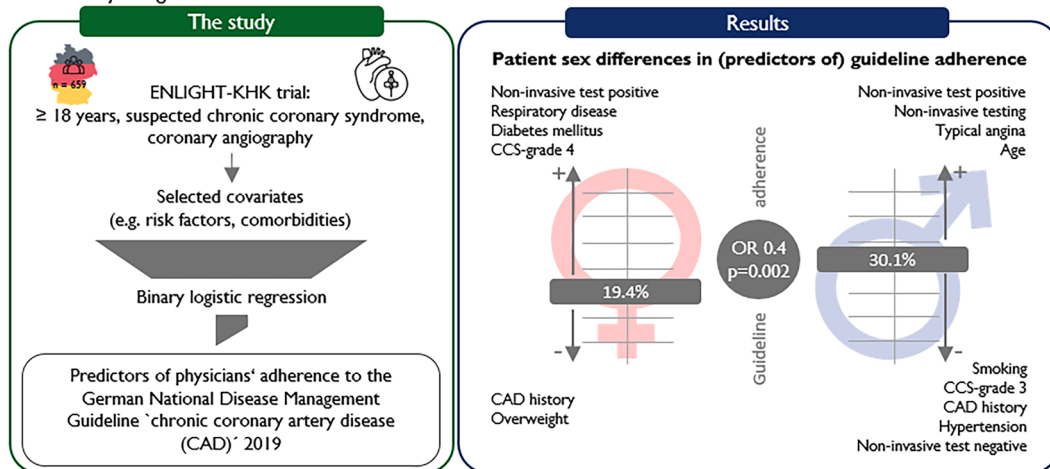
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Graphical abstract

Sex differences in guideline adherence for coronary angiography in patients with suspected chronic coronary syndrome in Germany: insights from the ENLIGHT-KHK trial



Keywords Coronary artery disease · Coronary angiography · Sex differences · Guideline adherence

Abbreviations

ACS	Acute coronary syndrome
CA	Coronary angiography
CAD	Coronary artery disease
CCS	Chronic coronary syndrome
CCS-Grade	Canadian Cardiovascular Society angina grade (classifies severity of angina)
CCTA	Coronary computed tomography angiography
CMR	Cardiac magnetic resonance imaging
ECG	Electrocardiogram
ECHO	Echocardiography
ESC	European Society of Cardiology
GNDMG	German national disease management guideline
MPS	Myocardial perfusion scintigraphy
OR	Odds ratio
PTP	Pre-test probability
SD	Standard deviation
SHI	Statutory health insurance

Background

Coronary artery disease (CAD) is the leading cause of death in Germany [1] for both women and men (2020: 86 and 179 deaths per 100,000 inhabitants) [2]. To reduce this high mortality rate, appropriate management is important. National and international clinical practice guidelines therefore provide evidence-based recommendations on the diagnosis and

treatment of CAD, for both the acute (acute coronary syndrome (ACS)) and the chronic (chronic coronary syndrome (CCS)) presentations of the disease [3–6].

In particular, an evidence-based diagnosis of CCS and the resulting prompt therapy might contribute to a reduction of morbidity and mortality and an improvement in quality of life among CAD patients [4, 6]. For diagnosing CCS, invasive coronary angiography (CA) is regarded as the reference standard [7]. However, CA as an invasive procedure is only recommended for patients considered for revascularization [4, 6]. Thus, an appropriate selection of eligible patients is essential. In the German National Disease Management Guideline (GNDMG) “Chronic CAD” of 2019, an algorithmic approach recommends a CA either for patients with an intermediate pre-test probability (PTP) of obstructive CAD (15–85%) and positive results in anatomical (coronary computed tomography angiography (CCTA)) or functional non-invasive testing (e.g. stress echocardiography (ECHO) or cardiac magnetic resonance imaging (CMR)), or for patients with a high PTP (> 85%) [4]. The PTP is estimated based on age, sex and the patient’s symptoms [4, 8, 9]. The 2019 European Society of Cardiology (ESC) guidelines on the diagnosis and management of CCS recommend a non-invasive test as an initial step for all patients for whom CAD cannot be excluded by clinical assessment [6].

There is increasing evidence from OECD countries that, in the management of ACS and the medical therapy for CCS, healthcare providers’ adherence to the guidelines is lower for women than for men [10–14]. This might contribute to the higher risk of death and acute myocardial infarction among

women with CAD compared to men [10, 12]. In contrast, little is known about patient-related sex differences in the guideline-adherent use of CA for suspected CCS [15].

For women with suspected CCS, a lower guideline adherence for CA increases the risk of being underdiagnosed (in cases of no CA despite indication) or exposed more often to the burden and risk of CA [16] (in cases of CA without indication) compared to men [4]. This could result in a higher morbidity and mortality and a reduced quality of life for women than compared to men.

This study aims to gain initial insights into sex differences in the guideline adherence for CA for suspected CCS in Germany. Using data from patients with suspected CCS who received a CA, two research questions were investigated: i) Is there a difference between the healthcare providers' guideline adherence for the use of CA in women with suspected CCS compared to men?, ii) Do the predictors affecting healthcare providers' guideline adherence differ between women and men with suspected CCS?

Methods

Study cohort

This study is a prespecified subanalysis of the German ENLIGHT-KHK trial, a multicentre, prospective, observational study that investigated the nature and extent of guideline adherence in the diagnostic workup of CA in patients with suspected obstructive CCS and evaluated the clinical and economic consequences of potential guideline non-adherence [17].

The ENLIGHT-KHK trial (2019–2021) included 901 adults who presented with suspected obstructive CCS with excluded ACS (i.e. unstable angina or acute myocardial infarction) to one of nine non-university hospitals in Germany, and who were assigned to or underwent a CA within the current admission [17]. Patients were included in different clinical settings and during different steps of the diagnostic workup, thus resulting in 5 cohorts [17]. These were: (1) patients referred for elective CA [18], (2) patients presenting at the emergency department who underwent CA [19], (3) patients presenting in the outpatient department without prior diagnostic workup, (4) patients presenting at the emergency department undergoing planned non-invasive testing, and (5) patients referred for elective, non-invasive image testing. This analysis included all patients of the ENLIGHT-KHK trial in whom adherence to the GNDMG “Chronic CAD” of 2019 was assessed, i.e. those with CA and sufficient data on PTP, symptoms and non-invasive test results. Of 695 patients with CA, guideline adherence could not be assessed in 36 patients due to missing data on angina

type and non-invasive test results, leading to a total of 659 patients who were included in this analysis [17, 20].

Study outcomes and data collection

To answer research question i), the difference in physicians' adherence to the GNDMG “Chronic CAD” of 2019 for CA between women and men was evaluated, together with the association between patient sex (i.e. self-reported biological sex [21]) and physicians' guideline adherence. In line with research question ii), the extent to which factors influencing physicians' guideline adherence for CA differed between women and men was investigated. For this purpose, the number, type, effect and impact of the predictors of guideline adherence were compared between women and men.

All the data were taken from the ENLIGHT-KHK trial (Table 1) [17, 20]. Guideline adherence was defined according to the GNDMG [4] and was evaluated using a priori defined rules based on data from patients' medical records and patients' questionnaires. These data included the patient's PTP [8, 9] for having an obstructive CAD and the results of the prior non-invasive testing (i.e. exercise electrocardiogram (ECG), stress ECHO, myocardial perfusion scintigraphy (MPS), CCTA and stress-CMR). PTP was calculated using the age and sex obtained from patients' medical records, while the type of anginal symptoms was obtained from a standardized patient questionnaire. Non-invasive testing and its results were obtained from patients' medical records [17]. For the rationale used to define guideline adherence, see Table 2 [20].

Furthermore, patient demographics, risk factors and comorbidities were obtained from patients' medical records, and data on the severity of symptoms were collected using a standardized patient questionnaire [17].

Statistical analyses

Baseline characteristics of the study population were reported using mean and standard deviation (SD) for continuous variables, and numbers and proportions for categorical variables. Characteristics were compared between women and men using a Chi-square test for categorical variables and a Mann–Whitney *U* test for continuous and ordinal variables. To assess the correlation between the PTP and obstructive CAD, Spearman's rank correlation coefficient (ρ) was calculated.

To answer research question i), firstly, a Chi-square test was conducted comparing the physicians' guideline adherence between both patient sexes. The results were presented as difference with a corresponding 95% confidence interval and *p* value. Secondly, a multiple binary logistic regression model was developed to investigate the adjusted association between patient sex and physicians' guideline adherence. Factors that

Table 1 Data sources and variables

Data source	Variables
Patients' medical record	Demographics: Sex Age Risk factors: Hypertension Diabetes mellitus ^a Smoking ^b Overweight ^c Hypercholesterolaemia Family history of CAD Comorbidities: CAD history ^d Chronic renal failure ^e Respiratory disease ^f Peripheral artery disease Depression Non-invasive testing: Exercise electrocardiogram Stress echocardiography Coronary computed tomography angiography Stress cardiac magnetic resonance imaging Myocardial perfusion scintigraphy Non-invasive test result ^g
Patient questionnaires	Type of anginal symptoms ^h Symptom severity ⁱ
Analysis results	Guideline adherence

CAD coronary artery disease

^aType 1 or 2^bEver/never^cBMI ≥ 25 ^dKnown CAD, myocardial infarction, catheterization without stent, revascularization^eDefined as an estimated glomerular filtration rate < 60 ml/min/1.72 m²^fChronic obstructive lung disease or other^gPositive (at least one test positive), negative (no test positive and at least one test negative), unclear (no test positive/negative and at least one test unclear)^hTypical angina, atypical angina, non-anginal chest painⁱCanadian Cardiovascular Society (CCS)-Grade 0–4

might influence physicians' decision-making on CA use were determined based on the literature and guidelines [4, 22, 23] and were verified by a clinical expert (BW). No interaction terms were included, since they would increase the complexity and reduce the interpretability of the models. The final set of covariates included age, type of anginal symptoms, symptom severity according to Canadian Cardiovascular Society classification (CCS-Grade), risk factors, comorbidities, non-invasive testing (i.e. at least one non-invasive test) and the test result (Model 1) as defined in Table 1. Since the ENLIGHT-KHK

trial determined guideline adherence based on the results of prior non-invasive testing (Table 2) [17, 20], variables including non-invasive testing and its result were expected to have a large influence on our analysis. To account for this and to analyse the change in explanatory power, a second regression model was fitted; this adjusted for the aforementioned covariates with the exception of non-invasive testing and its result (Model 2).

To answer research question ii), patient sex-specific predictors of physicians' guideline adherence were examined and compared by running both regression models separately for women (Model 1-f, Model 2-f) and men (Model 1-m, Model 2-m).

The models were developed by backward stepwise regression (details on the analysis are presented in Online Resource, Text S1). Regression model results were presented as an odds ratio (OR) with a corresponding 95% confidence interval and *p* value. Model performance was assessed using the pseudo- R^2 (Nagelkerke R^2) [24]. For all analyses, a *p* value < 0.05 indicated statistical significance. To account for multiple testing, the Benjamini–Hochberg procedure was used. All analyses were conducted with IBM SPSS Statistics for Windows, version 29, Armonk, NY: IBM Corp.

Results

Patient characteristics

A total of 659 patients were included, whose baseline characteristics are summarized in Table 3. On average, the patients were 67 ± 10 years old. The majority of the patients ($n = 495$, 75%) had three or more risk factors, with hypertension ($n = 549$, 83%) and overweight ($n = 519$, 79%) being the most common. More than one third of the patients presented with typical angina ($n = 224$, 34%) or received non-invasive testing prior to CA ($n = 237$, 36%). 273 patients (41%) were female and 386 (59%) were male. The women were older and less likely to be a current or former smoker or have a history of CAD ($p < 0.001$). Furthermore, the women tended to be less likely to receive non-invasive testing ($p < 0.05$ without Benjamini–Hochberg adjustment, see Online Resource, Table S1). CA identified obstructive CAD in 51% of women and 74% of men. The correlation between PTP and obstructive CAD was significant for men ($\rho = 0.135$, $p = 0.008$) but not for women ($\rho = 0.082$, $p > 0.05$).

Sex difference in guideline adherence and association between patient sex and guideline adherence (research question i))

Guideline adherence for CA was lower in women than in men (19.4% vs. 30.1%, difference [95% CI] 0.106 [0.04;0.17], $p = 0.002$, see Table 3).

Table 2 Definition of guideline adherence

Pre-test probability	Non-invasive testing ^a	Guideline adherence of coronary angiography
Low (< 15%)	Not done	No
	Non-pathological result	No
	Pathological result	Yes
	Inconclusive result	Yes
Intermediate (15–85%)	Not done	No
	Non-pathological result	No
	Pathological result	Yes
	Inconclusive result	Yes
High ($\geq 85\%$)	Irrespective of non-invasive testing	Yes

^aStress echocardiography, coronary computed tomography angiography, myocardial perfusion scintigraphy or cardiac stress magnetic resonance imaging

Regression models identified patient sex as a predictor of guideline adherence. According to Model 1, after adjusting for age, typical angina, diabetes mellitus, non-invasive testing, negative non-invasive test result and positive non-invasive test result, CAs were less likely to be guideline-adherent for women than for men (OR [95% CI] 0.40 [0.23;0.69], $p=0.002$). Model performance was high (Nagelkerke $R^2=0.628$).

After excluding non-invasive testing and its results (Model 2), the significant sex difference in guideline adherence remained. When adjusting for age, typical angina, hypertension, CAD history and CCS-Grade 3, CAs were less likely to be guideline-adherent for women than for men (OR [95% CI] 0.44 [0.30;0.66], $p<0.001$). Compared to Model 1, performance was lower in Model 2 (Nagelkerke $R^2=0.114$). Table 4 displays the results of the two regression models (see Online Resource, Tables S2: results before Benjamini–Hochberg adjustment and Tables S3: results of the first step of regression).

Sex differences in predictors of guideline adherence (research question ii)

In Model 1-f for women, five predictors of guideline adherence were derived; these explained up to 63% of the variation in guideline adherence ($p<0.001$, Nagelkerke $R^2=0.634$). While diabetes mellitus, a respiratory disease, CCS-Grade 4 and a positive non-invasive test result were associated with a higher probability of guideline-adherent CA, presenting with a CAD history was associated with a lower probability of guideline-adherent CA for women. Similarly, for men, six predictors of guideline adherence were detected and up to 61% of the variation in guideline adherence was explained by Model 1-m ($p<0.001$, Nagelkerke $R^2=0.613$). Predictors for men differed from those for women. For men, a higher age, a typical angina, prior non-invasive testing and a positive non-invasive test result were associated with a higher probability of guideline-adherent CA, whereas a negative

non-invasive test result and being a smoker were associated with a lower probability of guideline-adherent CA.

After excluding non-invasive testing and its results, the sex differences in predictor models of guideline adherence remained (Model 2-f vs. 2-m). For women, only two predictors were identified, and up to 6.6% of the variation in guideline adherence was explained by Model 2-f ($p=0.003$, Nagelkerke $R^2=0.066$). A CAD history and overweight were associated with a lower probability of guideline-adherent CA for women. In contrast, for men, six predictors of guideline adherence were detected, and up to 26% of the variation in guideline adherence was explained by Model 2-m ($p<0.001$, Nagelkerke $R^2=0.26$). While higher age and a typical angina were associated with a higher probability of guideline-adherent CA, presenting with hypertension, a CAD history or a CCS-Grade 3 was associated with a lower probability of guideline-adherent CA for men, as was being a smoker. The results of the regression models are presented in Table 5 (see Online Resource, Tables S2: results before Benjamini–Hochberg adjustment and Tables S3: results of the first step of regression).

Discussion

Based on data from the German ENLIGHT-KHK trial, physicians' adherence to guideline recommendations for CA use was lower for women with suspected CCS compared to men (19% vs. 30%). CAs were significantly less likely to be guideline-adherent for women than for men; this could not be accounted for by other factors such as age, anginal symptoms, risk factors, comorbidities or non-invasive testing alone (Model 1: OR 0.40, $p=0.002$; Model 2: OR 0.44, $p<0.001$).

Analyses confirmed that a model including non-invasive testing and its results (Model 1) explained guideline adherence more accurately than a model based on patient characteristics alone (Model 2). Furthermore, the underlying

Table 3 Baseline characteristics and coronary angiography results of participants

Characteristic	Total (n = 659)	Women (n = 273)	Men (n = 386)	<i>p</i> value ^a
Age (years), mean (SD)	66.5 (10.4)	68.9 (10.0)	64.8 (10.4)	< 0.001
BMI, mean (SD)	29.6 (5.9)	29.9 (6.4)	29.4 (5.5)	0.771
Number of risk factors; n (%)				0.522
0	6 (0.9)	2 (0.7)	4 (1.4)	
1–2	158 (24.0)	73 (26.7)	85 (22.0)	
≥ 3	495 (75.1)	198 (72.5)	297 (76.9)	
Cardiovascular risk factors; n (%)				
Diabetes mellitus	218 (33.1)	79 (28.9)	139 (36.0)	0.164
Smoking ^b	344 (52.2)	104 (38.1)	240 (62.2)	< 0.001
Overweight	519 (78.8)	212 (77.7)	307 (79.5)	0.712
Family history	210 (31.9)	98 (35.9)	112 (29.0)	0.164
Hypertension	549 (83.3)	236 (86.5)	313 (81.1)	0.164
Hypercholesterolaemia	366 (55.5)	150 (55.0)	216 (56.0)	0.840
Comorbidities; n (%)				
CAD history	335 (50.8)	114 (41.8)	221 (57.3)	< 0.001
Chronic renal failure	47 (7.1)	16 (5.9)	31 (8.0)	0.494
Respiratory disease	109 (16.5)	47 (17.2)	62 (16.1)	0.777
Peripheral artery disease	61 (9.3)	20 (7.3)	41 (10.6)	0.285
Depression	30 (4.6)	15 (5.5)	15 (3.9)	0.521
Type of anginal symptoms; n (%)				0.930
Typical angina	224 (34.0)	95 (34.8)	129 (33.4)	
Atypical angina	270 (41.0)	110 (40.3)	160 (41.5)	
Non-anginal thoracic constraints	165 (25.0)	68 (24.9)	97 (25.1)	
Symptom severity; n (%)				0.196
CCS-Grade 0	52 (7.9)	17 (6.2)	35 (9.1)	
CCS-Grade 1	110 (16.7)	36 (13.2)	74 (19.2)	
CCS-Grade 2	205 (31.1)	94 (34.4)	111 (28.8)	
CCS-Grade 3	230 (32.9)	99 (36.3)	131 (33.9)	
CCS-Grade 4 ^c	62 (9.4)	27 (9.9)	35 (9.1)	
Non-invasive testing; n (%)	237 (36.0)	86 (31.5)	151 (39.1)	0.164
Non-invasive test result ^d ; n (%)				0.669
Positive	130 (19.7)	43 (15.8)	87 (22.5)	
Negative	37 (5.6)	15 (5.5)	22 (5.7)	
Unclear	69 (10.5)	28 (10.3)	41 (10.6)	
Pre-test probability; n (%)				< 0.001
Low (< 15%)	14 (2.1)	14 (5.1)	0 (0.0)	
Intermediate (15–85%)	600 (91.0)	259 (94.9)	341 (88.3)	
High (≥ 85%)	45 (6.8)	0 (0.0)	45 (11.7)	
Coronary angiography				
Guideline-adherent	169 (25.6)	53 (19.4)	116 (30.1)	0.002
CAD	424 (64.3)	138 (50.5)	286 (74.1)	< 0.001

BMI body mass index; *CAD* coronary artery disease; *CCS* Canadian Cardiovascular Society; *SD* standard deviation

^aAll *p* values of baseline characteristics were adjusted using Benjamini–Hochberg procedure

^bEver (current or in the past)

^cPatients reporting symptoms at rest but without acute coronary syndrome

^dResult of one man missing

Table 4 Multiple binary logistic regression models for guideline adherence

Independent variable ^{c,d}	Model 1 ^a				Model 2 ^b			
	OR	95% CI	<i>p</i> value ^e	Nagelkerke R ²	OR	95% CI	<i>p</i> value ^e	Nagelkerke R ²
Sex	0.40 ^f	0.23–0.69	0.002	0.628	0.44 ^f	0.30–0.66	< 0.001	0.114
Age (in years)	1.09	1.06–1.12	< 0.001		1.04	1.02–1.06	< 0.001	
Diabetes mellitus	1.76	1.00–3.10	0.049					
Smoking								
Overweight								
Family history								
Hypertension					0.46	0.29–0.74	0.002	
Hypercholesterolaemia								
CAD history					0.58	0.39–0.85	0.008	
Chronic renal failure								
Respiratory disease								
Peripheral artery disease								
Depression								
Typical angina	4.72	2.63–8.47	< 0.001		1.96	1.35–2.86	< 0.001	
Atypical angina								
CCS-Grade 0								
CCS-Grade 1								
CCS-Grade 3					0.64	0.43–0.97	0.036	
CCS-Grade 4 ^g								
Non-invasive testing	33.06	15.33–71.29	< 0.001					
Non-invasive test result positive	5.72	2.77–11.78	< 0.001					
Non-invasive test result negative	0.13	0.04–0.40	< 0.001					

CAD coronary artery disease; CCS Canadian Cardiovascular Society; CI confidence interval; OR odds ratio

^aFinal model: Chi-square 366.980, *p* < 0.001

^bFinal model: Chi-square 53.215, *p* < 0.001

^cRedundant variables were excluded: non-anginal thoracic constraints, CCS-Grade 2, non-invasive test result unclear

^dfor sex: male sex as reference category; for all other variables: factor/disease not prevalent as reference category

^e*p* values were adjusted using Benjamini–Hochberg procedure

^fUnivariate OR: 0.71 (95% CI: 0.38–0.81)

^gPatients reporting symptoms at rest but without acute coronary syndrome

factors for PTP, i.e. age, sex and typical angina, were predictors in both models. However, diabetes mellitus (Model 1), hypertension and CAD history (Model 2) were identified as additional predictors.

Patient characteristics alone were more effective at explaining guideline adherence for men than for women (Model 2-m: Nagelkerke R² 0.260 vs. Model 2-f: Nagelkerke R² 0.066). Furthermore, while non-invasive testing and its result, age and typical angina were all predictors of guideline adherence for men, only a positive non-invasive test result had a strong impact among women. In addition to this, men's predictors included smoking, hypertension and CCS-Grade 3 (resulting in a lower probability of guideline adherence), whereas women's predictors included diabetes mellitus, respiratory disease, CCS-Grade 4 (resulting in a higher probability of guideline adherence) and overweight (resulting in a lower probability of guideline adherence).

CAD history was associated with a lower probability of guideline adherence for both sexes.

Comparison with other studies

Our result that CA use is less likely to be guideline-adherent when treating women with suspected CCS than men is in line with the published evidence. Leung et al. investigated adherence to US guidelines in referrals for CA with different indications in an Australian catheterization laboratory and concluded that women were more likely to undergo non-adherent CA than men (OR 2.67, 95% CI 2.24–3.19, *p* < 0.001) [15]. Further studies found that women with suspected CCS are less likely to be referred for CA [12, 22]. This suggests that women with suspected CCS undergo less CA, and when performed, their CAs are less likely to be guideline-adherent compared to men. This indicates an

Table 5 Multiple binary logistic regression models for guideline adherence, separated for women and men

Independent variable ^b	Women				Men			
	OR	95% CI	<i>p</i> value ^a	Nagelkerke R ²	OR	95% CI	<i>p</i> value ^a	Nagelkerke R ²
	Model 1-f ^c			0.634	Model 1-m ^d			0.613
Age					1.11	1.07–1.15	<0.001	
Diabetes mellitus	3.68	1.33–10.21	0.017					
Respiratory disease	3.13	1.06–9.23	0.041					
Smoking					0.48	0.25–0.92	0.032	
Typical angina					8.46	4.02–17.79	<0.001	
Non-invasive testing					14.19	5.49–36.71	<0.001	
Non-invasive test result positive	173.27	50.02–600.18	<0.001		7.94	2.97–21.22	<0.001	
Non-invasive test result negative					0.22	0.05–0.97	0.046	
CCS-Grade 4 ^e	4.40	1.23–15.71	0.028					
CAD history	0.23	0.08–0.68	0.013					
	Model 2-f ^f			0.066	Model 2-m ^g			0.260
Overweight	0.42	0.22–0.81	0.015					
Age					1.07	1.04–1.10	<0.001	
Smoking					0.55	0.34–0.91	0.024	
Typical angina					3.58	2.15–5.97	<0.001	
Hypertension					0.30	0.17–0.56	<0.001	
CAD history	0.48	0.25–0.93	0.032		0.52	0.31–0.86	0.016	
CCS-Grade 3					0.51	0.30–0.89	0.023	

CAD coronary artery disease; CCS Canadian Cardiovascular Society; CI confidence interval; OR odds ratio

^a*p* values were adjusted using Benjamini–Hochberg procedure

^bRedundant variables were excluded: CCS-Grade 2, non-invasive test result unclear, non-anginal thoracic constraints (men)/atypical angina (women)

^cFinal model: Chi-square 138.094, *p* < 0.001

^dFinal model: Chi square 218.580, *p* < 0.001

^ePatients reporting symptoms at rest but without acute coronary syndrome

^fFinal model: Chi-square 11.467, *p* = 0.003

^gFinal model: Chi-square 78.062, *p* < 0.001

inappropriate selection of women eligible for a CA across different countries and health systems.

In contrast, sex was not identified as a predictor of adherence to the ESC guidelines on the diagnosis and management of the chronic coronary syndrome in the ENLIGHT-KHK population [18]. One reason for this might be that the European recommendations for CA and non-invasive testing differ from the German recommendations. The GNDMG recommends non-invasive testing for patients with a PTP of 15–85% and direct CA for a PTP of > 85% [4]. Because only men can have a PTP of > 85% and only women can have a PTP of < 15%, the GNDMG recommendations depend on patient sex [4]. In contrast, the European guideline is based on downgraded PTP values (compared to previous values used in the GNDMG) [4, 6]. It recommends non-invasive testing as an initial measure for all patients for whom CAD cannot be excluded by clinical assessment, and thus does not depend on patient sex [6].

Potential reasons for sex differences in guideline adherence for CA

The lower adherence to the GNDMG when treating women compared to men may result from sex differences in the predictors of guideline adherence (indicating sex differences in physicians' decision-making process for CA use) caused by various potential reasons.

In our analysis, non-invasive testing and its results (both positive and negative) were predictive of guideline adherence for men, but only a positive test result was predictive for women. This might indicate a less frequent use of non-invasive testing when diagnosing women compared to men. One possible reason might be a lower diagnostic accuracy of some non-invasive tests in women. For example, in addition to the lower diagnostic accuracy for anatomic CAD of stress ECG and MPS compared to other non-invasive tests such as CCTA [25], a stress ECG is less sensitive and less specific in

women than in men due to a lower ability to perform physical exertion and hormonal factors. Furthermore, MPS results can be false positive in women, due to breast attenuation or smaller sized hearts [23, 26, 27]. This could result in a reduced confidence in non-invasive testing in women among physicians, even though diagnostic accuracy has been shown to be equivalent in women and men for other non-invasive tests (e.g. CCTA, CMR) [27, 28].

In our analysis, the type of anginal symptoms, age and smoking were only predictors for men. This might indicate that physicians are less likely to use these characteristics for decision-making for CA use in women. One possible explanation for this is the challenges physicians' face when determining the type of anginal symptoms for choosing an appropriate diagnostic option in women with often non-specific clinical symptoms of CAD (e.g. shortness of breath, fatigue) [28–30]. Furthermore, physicians might not take women's ages into account for decision-making, because women remain at intermediate PTP when aging that indicates non-invasive testing as an initial measure [4]. In contrast, older age can contribute to a high PTP in men, suggesting a direct CA [4]. In addition to this, smoking may be only considered among men due to physicians' knowledge that this important CAD risk factor is more prevalent in German men than women [31]. Although several studies have shown that smoking has a more detrimental effect for women than for men [29, 32, 33], physicians might assume a particularly high risk of CCS in male smokers and refer them directly for CA (i.e. non-adherent for men with $PTP \leq 85\%$ [4]).

In our analysis, overweight was only a predictor of guideline adherence for women, indicating that physicians may only use this characteristic for decision-making for CA use in women. One possible reason for this is the challenges related to performing some non-invasive tests in overweight patients, which increase the physicians' limited trust in non-invasive testing in women. In particular, the accuracy of exercise ECG, stress ECHO, MPS and CCTA is often limited in obese patients due to difficulties in exercising, poor signal to noise ratios and attenuation artefacts [34]. Although stress CMR is less affected by obesity [34], it is rarely available in an outpatient setting. This might lead to a referral of overweight women for direct CA (i.e. non-adherent [4]).

While hypertension and CCS-Grade 3 were associated with a lower probability of guideline adherence for men, diabetes mellitus, a respiratory disease and a CCS-Grade 4 were associated with a higher probability for women in our analysis. This might indicate that physicians assume a high likelihood of CCS in men with risk factors and strong symptoms, thus directly referring them for CA (i.e. non-adherent in men with $PTP \leq 85\%$ [4]). Women with such characteristics, on the other hand, may be suspected of having an intermediate likelihood, and receive non-invasive testing

first (i.e. adherent [4]). One reason for this might be that physicians assume a lower overall risk of CCS in women due to the lower prevalence of CAD in women compared with men [35]. This was also observed in our analysis (Table 3).

Our solely patient characteristic-based model included more predictors and could explain more precise guideline adherence for men compared to women (Model 2-m vs. 2-f). This might indicate a greater uncertainty of physicians in the diagnostic workup for women with suspected CCS than for men, corresponding to published evidence. For example, many physicians are unsure whether the standard cardiovascular risk prediction methods are equally effective for both sexes [36]. This is supported by our analysis, which observed a correlation between PTP and CAD for men, but not for women. To some extent, this is likely due to guideline recommendations and risk assessment models being predominantly derived from men and not sufficiently considering specific women's risk factors and clinical presentation [37–39].

However, the lower predictive power of Model 2-f could also indicate that guideline adherence for women depends on factors that are not considered in this analysis. For example, patient preferences [40, 41] could affect physicians' decisions on CA use.

Strengths and limitations

The main strength of this analysis is its prospective and multicentre data basis (i.e. the ENLIGHT-KHK trial).

However, some limitations should be considered when interpreting the results of this analysis. Firstly, since data collection was geared towards the aim of the ENLIGHT-KHK trial, not all of the factors that potentially affect guideline adherence for CA could be investigated. For example, patient preferences, organizational factors (e.g. accessibility and reimbursement of diagnostic procedures) and healthcare provider characteristics (e.g. physicians' attitudes or knowledge) might have altered the model results [40–42].

Secondly, it was not possible to investigate the influence of different non-invasive test types and their results on guideline adherence separately (because of the low number of tests). However, since guidelines recommend different non-invasive image-guided tests (e.g. stress CMR or CCTA) before a CA [4, 6], this should only have had a slight effect on the main results of this analysis.

Thirdly, since guideline adherence may differ depending on the specific healthcare setting and only nine hospitals were included in the analysis, the generalizability of the results for nationwide and international clinical practice may be limited. However, the study population seems comparable to the German national quality assurance cohort in terms of age, sex and body mass index (e.g. 41% vs. 37% women, 73% vs. 76% aged ≥ 60 years, 79% vs. 72% overweight) [43].

Finally, since all the ENLIGHT-KHK trial patients included in this analysis underwent a CA, it was not possible to evaluate patient-related sex differences in a potential underuse of CA (i.e. patients not receiving a recommended CA).

Implications and future directions

The observed guideline adherence has some consequences. An analysis based on the same population showed marginal negative clinical consequences (more major adverse cardiac events) and a non-negligible additional expenditure for the German Statutory Health Insurance (SHI) for the observed diagnostic workup compared to the complete, guideline-adherent version [20]. Based on the fact that guideline adherence was lower when treating women than men, the consequences of this might have a higher impact for women than for men.

Efforts are needed to reduce the differences between women and men in the evidence-based use of CA for suspected CCS. A number of different approaches are available for this. Firstly, examining and disseminating sex-specific disease characteristics, such as risk factors, predictors and pathophysiological mechanisms, could enable targeted management for women and men. For example, findings could contribute to more sex-specific guideline recommendations for the diagnostic workup of patients with suspected CCS. Secondly, disseminating evidence on the sex-specific diagnostic accuracy of non-invasive testing might improve acceptance and uptake among physicians of appropriate tests for women. Thirdly, enhancing awareness of CCS in women might ensure prompt and adequate diagnosis. Fourthly, further research could evaluate the association between guideline adherence for CA and other factors that were not investigated in our study (e.g. provider characteristics, structural conditions).

After the ENLIGHT-KHK trial, the GNDMG was updated in 2024. This updated version uses modified PTP values and strengthens the use of CCTA [44]. In addition, outpatient CCTA is reimbursed by the SHI from 2025 [45]. Since these changes might impact the clinical situation (e.g. increase the use of non-invasive tests), a reassessment of guideline adherence and potential sex-specific differences is recommended.

Conclusion

Based on the ENLIGHT-KHK trial population, women with suspected CCS are less likely to undergo a guideline-adherent CA than men, and predictors of guideline adherence differ noticeably between women and men. Our results contribute to the published evidence and may reflect limited

awareness and knowledge of CAD in women among health-care providers, as well as insufficiently sex-specific guideline recommendations.

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Data availability The datasets generated and/or analysed during the current study are not publicly available due to German data protection regulations (as they contain information that could compromise the privacy of research participants). However, aggregated data can be shared upon reasonable request.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Consent for publication Not applicable.

Ethical approval This study received a leading ethics approval (December 13, 2018) from the Ethics Committee of the Medical Association of North Rhine (Ärztchamber Nordrhein) (No. 2 018 361). Written informed consent was obtained from all the individual participants included in the study.

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Chapter 6

Key results

6 Key results

6.1 DP I: Prevalence and early detection of pre-heart failure

In the cross-sectional study of the HERZCHECK trial ($n = 4,509$), the pre-HF prevalence was 23% ($n = 1,023$). Besides male sex (odds ratio (OR) 4.2, $p < 0.001$), smoking (OR 1.4, $p < 0.001$), obesity (OR 1.5, $p < 0.001$), and diabetes (OR 1.7, $p < 0.001$) were associated with the presence of pre-HF¹.

The claims data analysis evaluating the early detection of pre-HF through GLS-based screening included 842 HERZCHECK participants with pre-HF and 8,420 participants in the historical control group. Participants were on average 60 years old, and 71% were male. Within the 9 years observation time (mean: 7 years per patient), weighted 20% of the individuals in the historical control group died, and 26% were diagnosed with HF, resulting in an HF incidence of 36 per 1,000 patient years. The weighted mean age at pre-HF diagnosis in HERZCHECK participants was 61 years, whereas HF was diagnosed at a weighted mean age of 68 years in SoC. Thus, the GLS-based screening detected pre-HF 7 years before a HF diagnosis in SoC (95% Confidence interval: 6.11 – 7.25 years, $p < 0.001$)¹.

The claims data analysis on differences in adverse events between those with and without pre-HF included 1,124 participants (282 without pre-HF, 842 with pre-HF). No difference in overall survival was observed between the groups, while the risk of HF events and HF hospitalizations was significantly higher in participants with pre-HF ($p < 0.05$)¹.

6.2 DP II: Health economic consequences of screening for pre-heart failure

Based on the 23% pre-HF prevalence observed in the HERZCHECK trial¹, the microsimulation model revealed additional benefits (0.10 QALYs and 0.12 LYs) and additional costs (€7,031) for a GLS-based screening in an at-risk population compared with SoC². This resulted in ICERs of €69,543/QALY and €59,552/LY. The ICER was lower when including only men (€52,379/QALY) or patients aged ≥ 60 years (€54,842/QALY). In addition, screening a population with a higher pre-HF prevalence or HF incidence would decrease the ICER. Taking into account medical advancement did not reveal an incremental OV in benefits, but incremental costs increased, resulting in a higher ICER².

In the deterministic sensitivity analysis, the costs of pre-HF and the HF incidence were the parameters with the largest impact on the results. According to the probabilistic sensitivity

analysis, the GLS-based screening is likely to result in additional benefits and costs compared with SoC, with the probability of cost-effectiveness increasing with the WTP. At a WTP of €30,000/QALY and €100,000/QALY, the screening was cost-effective with a probability of 29% and 67%, respectively².

6.3 DP III: Sex differences in guideline adherence for suspected coronary artery disease

The regression analysis on differences in the healthcare providers' guideline adherence for CA between women and men with suspected CCS included 659 participants from the ENLIGHT-KHK trial (41% female, average age of 67 years, 75% with three or more risk factors). Adherence to the recommendations for CA use of the GNDMG for chronic CAD of 2019 was lower for women than for men (19% vs. 30%, $p = 0.002$). In addition, patient sex was an independent predictor of guideline adherence, with CAs being less likely guideline-adherent in women (OR 0.4, $p < 0.05$). Predictors of guideline adherence differed between women and men with suspected CCS. For example, men's predictors included non-invasive testing and its results, age, and typical angina, of which only a positive non-invasive test result had a strong impact among women. In addition, models including only patient characteristics explained guideline adherence more accurately in men than women with suspected CCS³.

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Chapter 7

Discussion

7 Discussion

This cumulative dissertation explored opportunities and challenges of HF prevention and provides evidence to inform decision-making on the implementation of a structured GLS-based screening program in Germany. Relating to different determinants of HF prevention and using various methods of analysis, three DPs evaluated a GLS-based screening program for pre-HF in a German at-risk population (DP I and II), and analyzed sex differences in the guideline adherence for CA in the care of CCS (DP III). The results can be summarized as follows: i) a GLS-based screening program identified a 23% pre-HF prevalence in an at-risk population in north-east Germany¹, enables an early detection of pre-HF that provides almost seven years for preventive measures¹, and may be offered at an acceptable cost-effectiveness ratio²; ii) there are sex differences in the (predictors of) providers' guideline adherence for the diagnostic work-up for the most common cause of HF (i.e., CCS)³.

7.1 Comparison with the current state of research

7.1.1 Prevalence and early detection of pre-heart failure

Using a GLS-based screening, a 23% pre-HF prevalence was revealed in a German at-risk population in the HERZCHECK trial (DP I)¹. This is within the range of the highly variable estimates from literature⁴⁻⁶. A pooled analysis of three large community-based U.S. cohorts reported a pre-HF prevalence of 43%⁶. One reason for this higher estimate compared with that revealed in DP I¹ might be the broader definition of pre-HF, including various parameters such as LVEF, left ventricular mass, left atrial diameter, and BNP concentrations⁶.

A previous German cohort study (2013 to 2016) observed a pre-HF prevalence of 17%⁴. Although this study also used a broader pre-HF definition than the HERZCHECK trial (e.g., including a reduced LVEF, left ventricular hypertrophy or prior myocardial infarction), this estimate is slightly lower^{1,4}. An explanation might be the difference in the study populations. While the previous cohort study sampled from the general population in an urban region⁴, the HERZCHECK trial enrolled people at risk in structurally underserved regions (DP I)¹, which have a higher HF prevalence⁷.

Only one study (U.S., 2005 to 2010) was found that assessed a GLS-based pre-HF prevalence⁵. The slightly lower estimate (16%) compared with that of DP I may also be explained by the more urban population^{1,5}. In addition, by using ECHO for GLS assessment (which is less

accurate and feasible in obese patients^{8–10}), some persons with pre-HF might have been missed in the U.S. study that would have been detected using CMR¹.

No other studies were found that evaluated how much earlier pre-HF can be identified in a structured screening program compared with a HF diagnosis in SoC. However, the observed mean age of 61 years at pre-HF detection in a GLS-based screening (DP I)¹ is in line with published evidence. A Danish study observed the same mean age in women and men of the general population with a GLS comparable to HERZCHECK participants ($>-15.8\%$ vs. $\geq -15.5\%$)¹¹. Additionally, the aforementioned German cohort study observed a mean age of 63 years in patients with pre-HF⁴.

In contrast, compared with the mean age of 68 years at HF diagnosis in SoC observed in DP I¹, a mean age of 73 years was reported for an incident German HF population in 2021¹². This discrepancy might be due to differences in the patient population (i.e., no age limitation for study inclusion, lower HF risk), the definition of incident HF (i.e., one International Classification of Diseases (ICD)-code), and the data basis (i.e., no inpatient data) compared with DP I^{1,12}.

Evidence on the progression from pre-HF to HF is limited¹³. In the aforementioned Danish study, the HF incidence rate was lower than in DP I^{1,11}. Since the GLS was comparable between both populations, a potential reason might be the higher prevalence of other risk factors for HF onset¹⁴ in DP I (e.g., male sex: 71% vs. 49%, hypertension: 74% vs. 52%, diabetes: 37% vs. 10%)^{1,11}. Similarly, the HF incidence observed in the HERZCHECK control group (DP I)¹ was higher than in an U.S. stage B HF population with a lower prevalence of risk factors such as male sex (43%), hypertension (38%), and diabetes (8%)¹⁵.

In addition, the HF incidence in the at-risk population investigated in DP I was higher than that reported for the general German population^{1,16,17}. The positive association between HF incidence and age in DP I¹ is in accordance with published evidence^{18–21}. Similarly, a higher HF incidence in men compared with women was also observed in the Danish population with comparable GLS¹¹ and an U.S. population with pre-HF²².

7.1.2 Health economic consequences of screening for pre-heart failure

One study was found that evaluated the cost-effectiveness of a strain-based screening via CMR for early diagnosis of HF²³. By comparing a strain-based screening to standard ECHO from the payer perspective, this study resulted in a dominance of screening (i.e., lower costs and addi-

tional QALYs and LYs)²³. This deviates from the result of DP II². An explanation may be several methodological and conceptual differences compared with DP II^{2,23}, as presented in Table 2.

Table 2: Methodological and conceptual differences between Schneider et al., 2019²³ and DP II²

	Schneider et al., 2019²³	Kentenich et al., 2026² (DP II)
Healthcare system	U.S.	Germany
Population	Patients with pretest probability of early HF of 20% (determined by Charlson Comorbidity Score ≥ 3), aged 64 years, with or without previous HF hospitalization	Patients at-risk of HF (determined by presence of pre-defined risk factors), aged 40-69 years, without previous HF diagnosis
Model type	Cohort model	Microsimulation model
Cycle length	1 year	1 month
Intervention	Annual screening: Physical examination & strain analysis using CMR + therapy: medication & lifestyle modifications	One-time screening: GLS assessment using CMR + therapy: lifestyle modifications
Comparator	Physical examination & LVEF assessment using ECHO	No screening
Health states	stage B-D HF, death	Pre-HF (i.e., stage B HF), symptomatic HF (with or without hospitalization; i.e., stage C/D HF), death
Start distribution	stage B or C HF	Pre-HF (i.e., stage B HF)
Treatment effect	Reduction in HF hospitalizations	Reduction in HF incidence and mortality in pre-HF state
Costs	Outpatient visits, medication, imaging, procedural costs, HF hospitalization, palliative care	Outpatient visits, medication, imaging, lifestyle intervention, HF hospitalization
Definition of pre-HF	Not reported	GLS $\geq -15\%$
Sensitivity analysis	Deterministic	Deterministic and probabilistic

CMR = Cardiac Magnetic Resonance, DP = Dissertation Project, ECHO = Echocardiography, GLS = Global Longitudinal Strain, HF = Heart Failure, LVEF = Left Ventricular Ejection Fraction, U.S. = United States

Some studies evaluated the cost-effectiveness of different screening programs for pre-HF^{24–27}. Although the results are mostly in line with those of DP II and indicate a potential cost-effectiveness of a structured screening program^{24–26}, comparability is limited because the analyses differ in the following aspects:

- the screening and prevention approach (i.e., artificial intelligence electrocardiogram (AI-ECG) + medical therapy^{26,27}, BNP testing + ECHO + medical therapy²⁵, BNP testing + collaborative care²⁴, CMR + lifestyle intervention²)
- the definition of pre-HF (i.e., reduced LVEF^{26,27}, abnormal BNP level^{24,25}, impaired GLS²)
- the health system (i.e., U.S.^{25,26}, Ireland²⁴, Taiwan²⁷, Germany²)
- the target population (i.e., general population^{25–27}, at-risk population^{2,24})
- the study design (i.e., decision-analytic model^{2,25–27}, trial-based analysis²⁴)

7.1.3 Sex differences in guideline adherence in the care of chronic coronary artery disease

DP III indicated a lower healthcare providers' adherence to the GNDMG for chronic CAD (2019) for CA use in German women with suspected CCS than in men³. This is in line with existing evidence on guideline adherence in the care of CAD from Europe and Australia^{28–32}. One study of referrals for CA reported that women were more likely to undergo non-adherent CA than men²⁸. Similarly, women were less likely to receive guideline-indicated care (e.g., dual antiplatelet therapy)²⁹, and to achieve recommended blood pressure and lipid targets after an acute MI³⁰. In addition, guideline adherence for medication for confirmed CAD was lower in women than in men^{31,32}.

In contrast, sex-specific evidence on HF management is inconclusive, reporting either no sex differences or a lower likelihood of guideline-recommended care (e.g., medication) in women^{33–38}. Furthermore, no sex differences were observed in adherence to the European Society of Cardiology (ESC) guidelines on the diagnosis and management of CCS for CA use in the ENLIGHT-KHK population³⁹. This deviation to the results of DP III may be explained by recommendations of the ESC guideline independent of patient sex (in contrast to those of the GNDMG)^{3,40,41}. While the GNDMG recommends a CA for patients with a PTP >85% which only men can have⁴⁰, the ESC guideline recommends initial non-invasive testing for all patients with suspected CAD⁴¹.

Potential reasons for the observed sex differences in the guideline adherence for CA use are manifold: a lower healthcare providers' confidence in the diagnostic accuracy of some non-

invasive tests in women; differences in the prevalence of CCS and risk factors between women and men; differences in the clinical presentation between women and men; healthcare providers' uncertainty in the diagnostic workup for women with suspected CCS due to insufficiently sex-specific guidelines³.

7.2 Methodological strengths and limitations

7.2.1 Strengths

The overall strength of this dissertation lies in considering different determinants of HF prevention (i.e., early detection of pre-HF, cost-effective screening, guideline-adherent care of individuals at risk) and using various methods of analysis (i.e., descriptive statistics, weighted comparison of means, health economic modelling, regression analysis). Thereby, it provides evidence beyond the one-dimensional evaluation of an intervention and allows for a multifaceted exploration of both opportunities and challenges of HF prevention.

A further strength relates to the data base of the HERZCHECK trial. By i) including $\geq 4,500$ trial participants and $\geq 8,400$ historical control participants, and ii) combining primary and secondary data, it provides a valuable dataset for evaluating a GLS-based pre-HF screening program (DPs I and II)^{1,42}. Similarly, the ENLIGHT-KHK trial underlying DP III³ followed a prospective study design and transparently assessed guideline adherence^{39,43}.

In addition, to provide valuable information for allocation decisions of the German SHI, the comparative health economic evaluation (DP II) followed common recommendations for modelling^{44–50} that ensured the reliability of the results². For example, a thorough evaluation of uncertainty was conducted using deterministic and probabilistic sensitivity analyses^{2,48}, and a model validation was performed according to the 'Assessment of the Validation Status of Health Economic decision models' checklist^{2,51}. Furthermore, by using a microsimulation model the individual pathways of the targeted at-risk population could be considered^{2,45,47,49,52}.

Lastly, in contrast to most health economic evaluations targeting life extending treatments, an OV approach was added. By incorporating the OV, the model developed in DP II considered technological progress in medicine and thus, the patients' opportunity to benefit from expected future innovations during the extended life^{2,53}.

7.2.2 Limitations

Some limitations must be taken into account when interpreting the results of this dissertation. While specific limitations to the DPs are discussed in detail in the respective scientific publications presented in chapter 5, the main limitations are summarized as follows:

For reasons related to the data used for the analyses, the results of the DPs are subject to a certain degree of uncertainty. Firstly, since the HERZCHECK trial did not provide long-term data and all participants received the CMR screening⁴², the time gained for prevention had to be investigated using a historical control group (DP I)¹. Although the comprehensive statistical balancing should ensure comparable cardiovascular risks between the historical control group and the trial participants, confounding cannot be excluded. For example, (unknown) differences in the GLS distributions or other clinical parameters (e.g., blood pressure) between both groups may have affected the results¹.

Secondly, HF hospitalizations and HF events of HERZCHECK participants in DP I might be overestimated since both main and secondary inpatient diagnoses were included¹. However, since the definition applied to participants with and without pre-HF, this should not have influenced the results on differences between both groups¹.

Thirdly, since the HERZCHECK trial did not evaluate the long-term effect on patient-relevant outcomes and no structured lifestyle intervention was provided⁴², the health economic evaluation (DP II) had to rely on a literature-based clinical benefit². However, the effect measure was obtained from a large systematic review of RCTs (i.e., highest evidence level⁵⁴) on behavioral counseling interventions in patients at risk of cardiovascular disease^{2,55}.

Fourthly, because the regression analysis on sex differences in guideline adherence was a secondary analysis of ENLIGHT-KHK trial data, it could not consider all potential factors affecting guideline adherence (DP III)³. For example, patient preferences or organizational factors may have significantly altered the results^{3,56,57}.

Furthermore, with regard to all subprojects, generalizability of the results may be limited. Since the HERZCHECK trial targeted structurally underserved regions in north-east Germany⁴², the results of DP I and II may not be transferrable to other regions, particularly more urban regions^{1,2,42}. Similarly, the ENLIGHT-KHK trial only enrolled participants from nine non-university hospitals in Germany⁴³. As guideline adherence may depend on the healthcare setting, the results of DP III may not be generalizable for nationwide or international clinical practice³.

7.3 Opportunities and challenges for heart failure prevention

By identifying a pre-HF prevalence of almost one fourth in a German at-risk population¹, the findings of this dissertation confirm the need for a pre-HF screening program (chapter 2.2). A structured GLS-based screening program may be a promising approach searched for (chapter 2.3). Using a quantitative cardiac imaging marker assessed via telemedically-supervised CMR enables a low-risk⁵⁸ screening of many of people, even in structurally underserved regions¹. Thereby, it can detect pre-HF several years before a HF diagnosis in SoC, providing a large time span for preventive measures¹. Provided that patients at increased risk will be offered effective prevention and they make use of the preventive measure, the screening program may result in additional (quality adjusted) life years at an acceptable cost-effectiveness ratio². Since preventive lifestyle interventions assumed in the model may have an impact on the overall cardiovascular risk and also prevent other diseases (e.g., diabetes)^{55,59,60}, these benefits might even be higher than estimated in DP II².

However, with regard to limited healthcare resources (chapter 2.3) some challenges remain. Firstly, the evaluated GLS-based screening program may not be specific enough yet. For example, the 23% pre-HF prevalence resulted in high screening costs per detected case that outweighed cost savings from avoided diseases². In addition, although claims data analyses from historical controls are somewhat uncertain (chapter 7.2), and the GLS appears as promising marker for the onset of HF (chapter 2.3), the 26% HF incidence observed in the weighted historical control group¹ indicates that many of the screen-detected pre-HF patients may get symptomatic after more than nine years or never at all. Thus, an intervention and pre-HF management in all detected patients could be questionable from the perspective of the SHI. This is supported by the microsimulation model that resulted in too few HF cases prevented or delayed and too high accumulating pre-HF costs for cost savings compared with SoC². As seen in sensitivity analyses, the cost-effectiveness would improve for populations with higher rates of HF incidence and/or pre-HF prevalence².

Secondly, the health economic results are associated with some uncertainty². In particular, although the effect of lifestyle interventions in populations at cardiovascular risk used in the model may be transferable, the long-term clinical effect of GLS-based screening and prevention measures on patient-relevant outcomes is still unclear^{1,2,42}. Furthermore, pre-HF costs, which were the most sensitive model parameter, were based on a pre-post comparison² that could not control for confounders^{61,62}.

Thirdly, with expected medical advances in HF management, a GLS-based screening may not result in an incremental OV but incremental costs, increasing the ICER².

Beyond the aforementioned opportunities and challenges directly related to a GLS-based screening program, this dissertation also emphasizes critical aspects of guideline adherence as central determinant of effective prevention (chapter 2.3). Sex differences in the guideline adherence for CA were revealed in patients with CAD (i.e., the most common cause of HF^{63,64})³, which could impair HF prevention, particularly in women. Although the reasons are yet to be evaluated, this may reflect limited awareness or knowledge of sex differences in CAD and insufficiently sex-specific guidelines³. Evidence on sex differences could enable the development of targeted interventions to improve guideline adherence in women and men at risk of HF.

7.4 Implications for research, policy, and practice

The findings of this dissertation implicate a need to raise awareness of pre-HF in research, clinical practice, and policy. With a 23% pre-HF prevalence based on the GLS¹, this rate may be considerably higher when including other established criteria (chapter 2.1)^{14,65}.

While the AHA proposed the HF stages in 2001⁶⁶, they have not yet been part of the CPG of the ESC and the GNDMG for chronic HF^{18,19}. Considering the HF stages in recommendations of European CPGs could raise the awareness of the pre-clinical HF stages (i.e., stage A and B¹⁴) in clinical practice. Concurrently, decision-making for adequate care^{67,68} of affected patients will be supported. While there are several recommendations for pre-HF management that are based on high- and moderate-quality evidence, recommendations on pharmaceutical pre-HF therapy are limited for patients with preserved LVEF¹⁴. Thus, further research, particularly on pharmaceutical preventive measures, should be supported⁶⁹.

To improve cost-effectiveness, the GLS-based screening program evaluated in this dissertation has to be adjusted. GLS-based screening of all patients aged 40-69 years who have at least one pre-defined risk factor (i.e., diagnosis of hypertension/diabetes mellitus/hypercholesterolemia/chronic kidney disease/obesity or tobacco consumption) is associated with a small health gain only but considerable incremental costs compared with SoC (DP II)². Since this partially results from high costs per detected case, a more precise screening population receiving a CMR examination (i.e., a population with higher pre-HF prevalence) can increase cost-effectiveness. Further research should evaluate how to identify populations with high pre-HF prevalence more precisely using additional administrative (e.g., ICD Codes) or medical data (e.g., ECHO results) in addition to the six risk factors mentioned above².

Similarly, another explanation for failing a more favorable ICER is in the low number of HF cases prevented or delayed². To improve the identification of patients at high risk of HF

onset who are offered preventive measures, the pre-HF definition could be extended by additional variables. For example, further cardiac function parameters (e.g., BNP) or patient characteristics (e.g., age, comorbidities) could be added to the GLS. Therefore, further research on predictors adding incremental value for the prognosis of HF onset should be supported².

Since health economic decisions made under uncertainty are inferior compared with decisions with additional information⁷⁰, further research is needed to increase the robustness of the health economic results (DP II). For example, prospective trials should evaluate the long-term effect of GLS-based screening and prevention measures in pre-HF patients on patient-relevant outcomes². In particular, RCTs would provide high-quality evidence on the effectiveness⁷¹. Building up on the HERZCHECK trial⁴², extending the observation period, investigating patient-relevant outcomes (e.g., HF, mortality), and providing a structured lifestyle intervention would be essential. Besides traditional lifestyle interventions, behavioural economics interventions could be investigated. Since behavioural economics interventions account for the fact that human behaviour is often not always rational and affected, for example, by inconsistent preferences, norms, and emotions⁷², their inclusion may enhance the extent and sustainability of lifestyle adaptations.

In addition, pre-HF costs should be calculated by comparing costs of patients with and without pre-HF (since they were a highly influential input parameter of the microsimulation model)². Therefore, collecting real-world cost data would be useful to prevent from overestimation due to protocol-induced resource use in RCTs⁷³.

To ensure evidence-based care provided to patients at risk of HF, guideline adherence should be paid more attention. In particular, sex-specific analyses should be performed since they may reveal differences in guideline adherence and its predictors between women and men³. Knowledge about sex-differences in guideline adherence and their reasons enables researchers to develop targeted interventions for improving guideline adherence and medical outcomes in patients at risk of HF.

Interventions could include adjustments of guideline recommendations to take into account potential sex-specific disease characteristics. For example, guidelines for the diagnostic workup in patients with suspected CCS could consider sex differences in CAD risk factors and predictors^{3,74,75}. Similarly, sex differences in traditional risk factors (e.g., obesity, diabetes) and the pathophysiology of HF⁷⁶⁻⁷⁸ may be included in recommendations for pre-HF management. In addition, disseminating sex-specific evidence and raising awareness of HF and CAD in both sexes could improve evidence-based care in women and men³. This is supported by the German

Society of Cardiology in its recently published position paper on sex-specific aspects of cardiovascular diseases³⁸.

Since there are still large knowledge gaps and current guidelines are predominantly based on data derived of men^{38,74,77,78}, further research on sex-specific characteristics of the diseases is needed to develop such interventions. In addition, qualitative research on barriers and facilitators for CPG implementation^{56,57} is essential to examine underlying reasons for sex-specific differences in guideline adherence³.

To support the overarching goal of improving HF prevention, it is vital for healthcare policy to establish support mechanisms. These could include further research funding, for example, within the innovation funds of the federal joint committee, which funded both projects underlying this dissertation (Herz-Check: grant number 01NVF19014, ENLIGHT-KHK: grant number 01VSF17011). Furthermore, approaches to improve evidence-based care for all patients at risk of HF might be promising. These may be, for example, public awareness programs, education programs for healthcare providers and patients, financial incentives, improvements of guidelines, or quality assurance programs^{69,79,80}. Dedicated prevention implementation committees such as that of the European Association of Preventive Cardiology⁸⁰ and international initiatives such as the European joint action on cardiovascular diseases and diabetes (JACARDI)⁸¹ could enhance the development and implementation of such approaches. In addition, the findings of this dissertation encourage legal initiatives such as the proposal for the German “Gesundes-Herz-Gesetz” (healthy heart law) aiming at preventing cardiovascular diseases⁸², and may inform discussions on specific preventive approaches.

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Chapter 8

Conclusion

8 Conclusion

Due to the increasing clinical and economic burden of HF, HF prevention is gaining increasing importance. This cumulative dissertation explored opportunities and challenges of HF prevention and provides evidence to inform decision-making on the implementation of a structured GLS-based pre-HF screening program in the German healthcare system. Three DPs evaluated the diagnostic potential of a structured GLS-based pre-HF screening program (DP I), analyzed its cost-effectiveness (DP II), and examined sex differences in (predictors of) healthcare providers' guideline adherence for CA in the care of CCS (DP III).

The 23% pre-HF prevalence observed in the German risk population emphasizes the importance of increasing awareness of pre-HF and providing a structured screening program. By enabling a detection of pre-HF several years before a HF diagnosis in SoC and improving life expectancy compared with no screening, a GLS-based screening program as evaluated in this dissertation appears as a promising approach. However, it was associated with additional costs compared with SoC in the health economic model.

Further research is required to improve cost-effectiveness and ensure a successful implementation. In particular, the target population need to be specified to decrease screening costs per detected person. In addition, further pre-HF criteria besides the GLS should be investigated to enable a more precise assessment of the individual HF risk, and to offer preventive measures for those at particularly high risk. This would increase the number of HF cases prevented or delayed. In addition, prospective trials have to evaluate the long-term effects of structured lifestyle interventions on patient-relevant outcomes in pre-HF patients, and real-world data on pre-HF costs should be collected to improve the robustness of results.

Besides demonstrating the diagnostic and economic potential of a structured GLS-based pre-HF screening program, the results of this dissertation enhance the evaluation of guideline adherence in women and men at risk of HF. Investigating sex differences and their reasons enables the development of targeted interventions to improve evidence-based care and thus, HF prevention. Such interventions may include, for example, sex-specific adjustments of CPGs, disseminating sex-specific evidence, and raising awareness of HF and its risk factors in women and men. Therefore, further sex-specific research should be supported.



Appendix

Supplementary material to chapter 5.1 (DP I)

The supplementary material presented in this appendix has been previously published in ‘Circulation: Heart Failure’ (2026, 19:e013935, doi:10.1161/CIRCHEARTFAILURE.125.013935).

HERZCHECK: Early Detection of Subclinical Heart Failure Using Mobile Cardiac Magnetic Resonance and Telemedicine in Rural and Underresourced Regions: Supplemental Material

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1. Supplemental Methods

Methods S1: Methodological details for matching and entropy-balancing of the control cohort

The control cohort (CC) was obtained from claims data of the participating health insurance fund (AOK Nordost). It was built to have a comparable cardiovascular risk profile to a subgroup of the HERZCHECK cohort that included all participants diagnosed with subclinical pre-heart failure (pre-HF), who were insured at the AOK Nordost, lived in Mecklenburg-Western Pomerania (MVP) or Brandenburg (BB) at the end of the year of the cardiac magnetic resonance (CMR) (according to claims data), and consented to the analysis of their claims data. Therefore, first, the AOK Nordost conducted an exact matching (1:10) based on sex, age (in categories), region of residence (i.e., federal state and classification in urban, semi-urban, rural), and presence of at least one HF risk factor (i.e., hypertension, hypercholesterinemia, diabetes mellitus, chronic kidney disease, obesity) as defined in Supplemental Table S1. People were eligible for the CC if they were 40 to 70 years old, lived in MVP or BB at the end of 2013, and had a continuous insurance (i.e., at least one day per quarter) from January 1st 2012 to December 31st 2022 or death (whatever occurred first). Exclusion criterion was a HF diagnosis in 2012-2013 to ensure that only people at risk were considered. Second, the evaluators conducted a weighting procedure to further optimize covariate balance between the matched HERZCHECK participants and the CC. For the weighting procedure, entropy balancing, as described by Hainmueller et al.²², was applied. Covariates included sex, age, region of residence, risk factors, psychological diseases, Charlson Comorbidity Index (CCI)^{23,24}, healthcare costs, participation in relevant disease management programs and statin intake as defined in Supplemental Table S1. All variables were determined based on claims data of the year 2013 for CC participants and of 12 months before the CMR for HERZCHECK participants. For HERZCHECK participants, the CMR date from the HERZCHECK trial data was linked to the claims data via the HERZCHECK trial pseudonym, birth year and sex.

A detailed definition of the criteria used for matching and entropy balancing is presented in Supplemental Table S1.

To identify participants with risk factors, the following ICD-10 codes were used²⁵:

Hypertension: I10.0 – I10.1, I10.9, I15.0 – I15.2, I15.8 – I15.9

Hypercholesterolaemia: E78.0 – E78.1

Obesity: E66.0 – E66.2, E66.8 – E66.9, E67.8, E68

Diabetes mellitus: E10 – E14
 Chronic kidney disease: N18 – N19

To identify participants with psychological diseases the following ICD-10 codes were used²⁵:

F00-F09: Organic, including symptomatic, mental disorders
 F10-F16, F18, F19: Mental and behavioral disorders due to psychoactive substance use
 F20-F29: Schizophrenia, schizotypal and delusional disorders
 F30-F33: Mood (affective) disorders: manic episode, bipolar affective disorder, depressive episode, recurrent depressive disorder
 F70-F79: Mental retardation

Baseline characteristics (obtained from claims data) of the matched HERZCHECK and CC participants were reported using numbers and proportions for categorical variables, and means and standard deviations for continuous variables. Characteristics were compared between HERZCHECK participants and the CC using absolute standardized mean differences (ASMD). All claims data were thoroughly checked for integrity and plausibility. Duplicates were removed and negative costs (i.e., cancelled inpatient cases that were not reimbursed by the AOK Nordost) were set to zero in consultation with the AOK Nordost.

Methods S2: Details on the evaluation of adverse events in the HERZCHECK subgroup

HF-Hospitalizations, HF and all-cause mortality within 12 months after the CMR were evaluated based on AOK Nordost claims data of all HERZCHECK participants who were followed after the CMR (i.e., 10% of participants without pre-HF, all participants with pre-HF) and were insured at the AOK Nordost. Thereby, HF hospitalizations were defined as hospital admission with a corresponding main or secondary diagnosis. HF was defined as any hospitalization with main or secondary diagnosis, or any new (i.e., no inpatient or outpatient diagnosis within 24 months before the CMR) secured outpatient diagnosis. A HF diagnosis was defined as ICD-10 Codes I11.0, I13.0, I13.2 and I50. To compare HERZCHECK participants with and without pre-HF, the CMR date and the screening result (GLS $\geq$ -15%: subclinical pre-HF or GLS $<$ -15%: no subclinical pre-HF) from the HERZCHECK trial data were linked to the claims data via the HERZCHECK trial pseudonym, birth year and sex.

Events were presented as numbers and proportions for those with preserved GLS and those with subclinical pre-HF. In addition, survival was calculated and displayed using the Kaplan-Meier

method^{26,27}. Differences between participants with preserved GLS and those with subclinical pre-HF were assessed using the log-rank test. For all analyses, a p-value <0.05 indicated statistical significance. All analyses were conducted with R, version 4.4.1, R Foundation for Statistical Computing, Vienna, Austria. All claims data were thoroughly checked for integrity and plausibility. Duplicates were removed in consultation with the AOK Nordost.

Methods S3: Methodological details for evaluating time gained for prevention

To evaluate whether the HERZCHECK screening enables an early detection of subclinical pre-HF, it was tested for a difference in age at subclinical pre-HF/HF detection between the matched HERZCHECK and CC participants. Therefore, claims data of the AOK Nordost were collected for the CC and HERZCHECK participants with subclinical pre-HF, who were insured at the AOK Nordost. Claims data included patient demographics, data on outpatient and inpatient care, and data on medication. The data covered a patient-specific period of 24 months prior to 12 months after the CMR for HERZCHECK participants and ranged from January 1st, 2012, to December 31st, 2022, or death (whichever occurred first) for the CC. For HERZCHECK participants, the CMR date from the HERZCHECK trial data was linked to the claims data via the HERZCHECK trial pseudonym, birth year and sex. Age at subclinical pre-HF detection was defined as age of HERZCHECK participants with subclinical pre-HF at the CMR. Age at HF detection was defined as age of CC participants at the first validated HF-diagnosis (i.e., incident HF-diagnosis) documented in the claims data. A definition of a validated HF-diagnosis is provided in the Supplemental Methods S4.

It was tested for a difference between age at subclinical pre-HF detection in the HERZCHECK participants and the age at HF detection in the CC using weighted t-test, with p-values presented. Further, the mean difference and corresponding 95% confidence interval were reported. In addition, to evaluate how many HERZCHECK participants with screen-detected subclinical pre-HF would have been diagnosed in SoC, the number and proportion of incident HF cases in the CC and the HF incidence rate per 1,000 patient years was calculated. Therefore, CC participants were followed from January 1st, 2014, to December 31st, 2022, or death (defined as end of the last insurance period before December 31st, 2022; whichever occurred first). For all analyses, a p-value <0.05 indicated statistical significance. To account for multiple testing, the Benjamini-Hochberg procedure was used. All analyses were conducted with R, version 4.4.1, R Foundation for Statistical Computing, Vienna, Austria. All claims data were thoroughly

checked for integrity and plausibility. Duplicates were removed in consultation with the AOK Nordost.

Methods S4: Details on HF-diagnosis validation for evaluating time gained for prevention

To identify participants with incident HF, the following ICD-10 diagnoses were used²⁵:

I50 Heart failure

I13.0 Hypertensive heart and renal disease with (congestive) heart failure

I13.2 Hypertensive heart and renal disease with (congestive) heart failure and renal failure

I11.0 Hypertensive heart with (congestive) heart failure

Due to possible incorrect or biased coding or a lack of recording of diagnoses²⁸, an internal diagnosis validation was conducted. A HF diagnosis was considered as validated in the following cases^{29–31}:

≥ 1 inpatient main or secondary diagnosis

≥ 2 secured outpatient diagnoses within two quarters in one year

≥ 2 secured outpatient diagnoses by ≥ 2 health care providers within one quarter

1 secured outpatient diagnosis + HF related medication within the same or the following quarter

1 secured outpatient diagnosis + HF-telemonitoring by the diagnosing health care provider within the same or the following three quarters

Thereby, HF related medication included Angiotensin-Converting Enzyme Inhibitors (ACEI), Angiotensin II receptor blocker (ARB), beta blockers (BB), Diuretics. These substance groups were selected because they are recommended for almost all HF participants³². A prescription of these substances was defined via the following Anatomical Therapeutic Chemical (ATC) classification codes:

ACE-inhibitors: C09A, C09B

ARB: C09C, C09D

Beta blockers: C07

Diuretics: C03

HF-telemonitoring was defined via the Codes of the Doctors' Fee Scale (Einheitlicher Bewertungsmaßstab – EBM) 03325, 03326 and 13578-13587^{28,30,33}.

Methods S5: Methodological details of sensitivity analyses and subgroup analyses for evaluating time gained for prevention

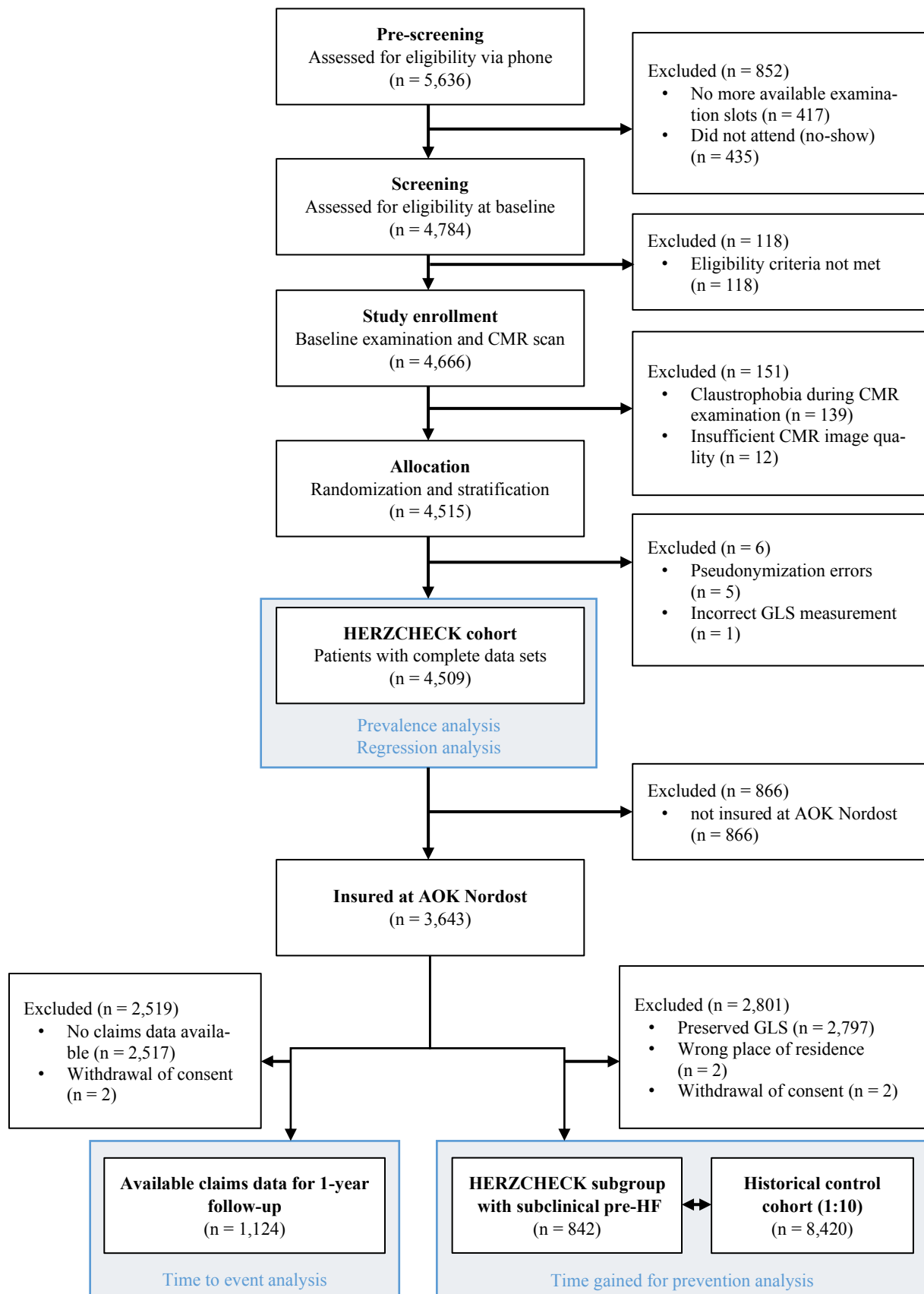
Subgroup analyses were conducted to evaluate whether results differed according to sex, region of residence, and age (for evaluating HF incidence only).

To test the robustness of the results, the following sensitivity analyses were conducted (i) to vi) for evaluating time gained for prevention; i) and ii) for evaluating the HF incidence in the CC):

- i) requiring secondary inpatient diagnoses to be validated by an outpatient diagnosis
- ii) defining two outpatient diagnoses as validated only if documented in two consecutive quarters
- iii) including cases beginning before or ending after the baseline-period (instead of only cases beginning before the baseline-period) for calculating costs
- iv) using rounded age of HERZCHECK participants for entropy balancing
- v) conducting entropy balancing only for CC participants with incident HF
- vi) using more conservative age at diagnosis (i.e., assuming the birthday at the beginning of the birth month for the HERZCHECK participants and at the end of the birth month for the CC participants).

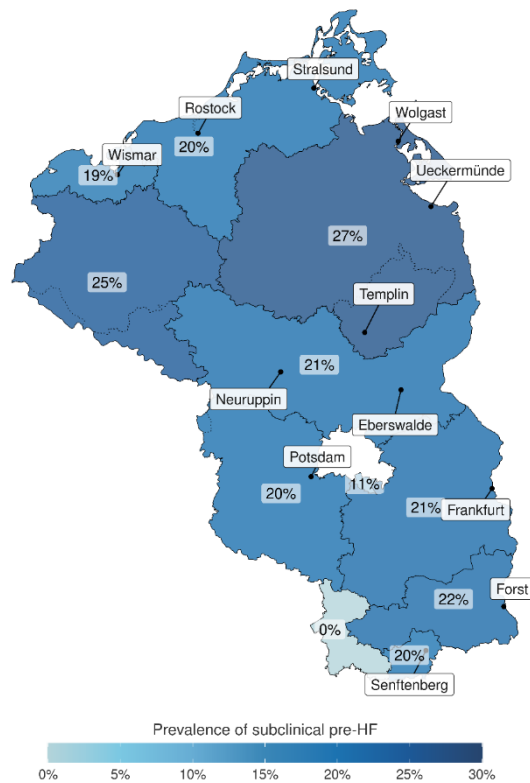
2. Supplemental Figures

Figure S1: Flowchart displaying the recruitment process (entire HERZCHECK cohort)



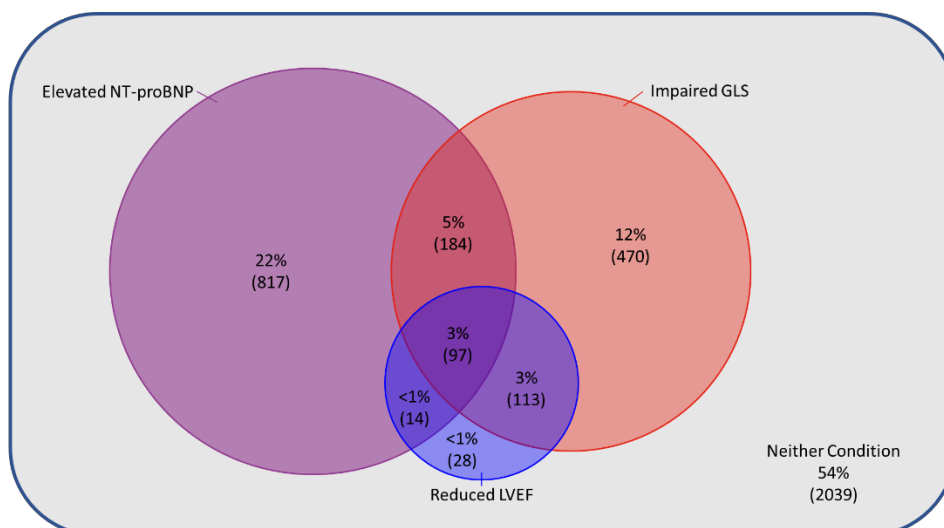
CMR = Cardiac Magnetic Resonance, GLS = Global Longitudinal Strain, HF = Heart Failure

Figure S2: Regional distribution of subclinical pre-heart failure in the evaluated rural and underresourced areas of Germany



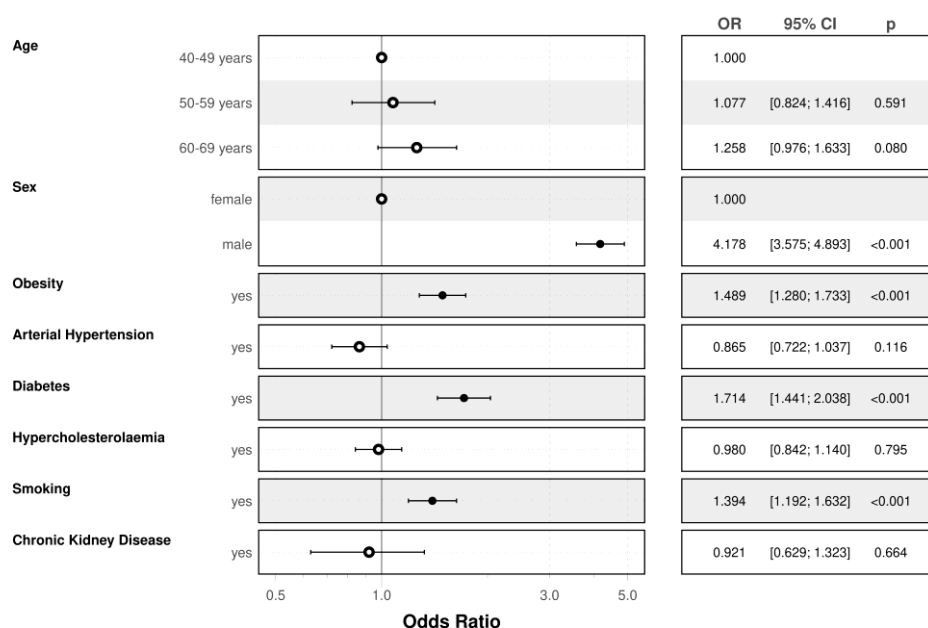
HF = Heart Failure, GLS = Global Longitudinal Strain

Figure S3: Venn-diagramm demonstrating the relationship between GLS-based subclinical pre-HF to preserved or reduced LVEF and normal or elevated NT-proBNP levels



Overlap of abnormal NT-proBNP, impaired GLS, and reduced LVEF. Values represent absolute counts and percentages of the total cohort (N = 3,762). The sizes of the circles are proportional to group size; overlaps are schematic.

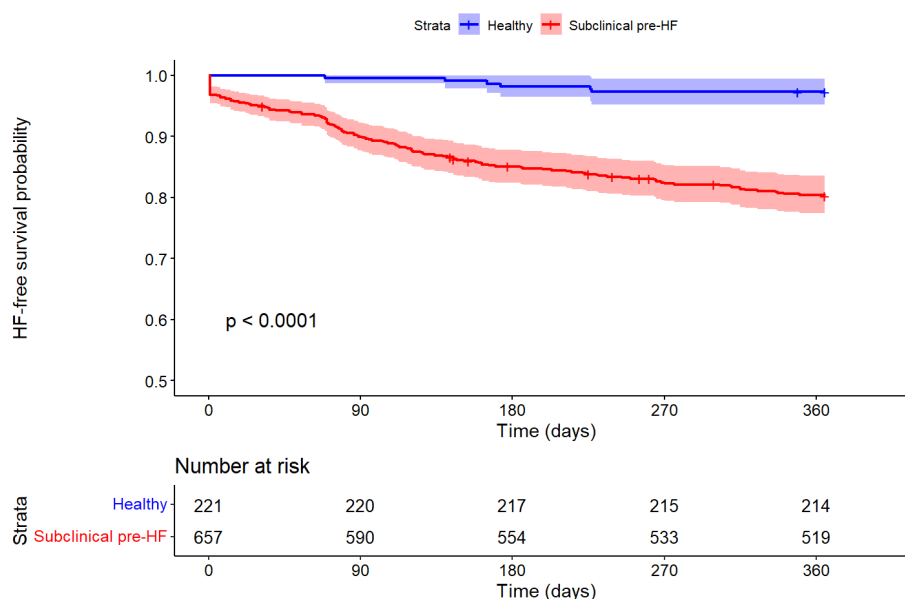
GLS = Global Longitudinal Strain, LVEF = Left Ventricular Ejection Fraction, NT-proBNP = N-terminal pro-B-type natriuretic peptide

Figure S4: Results of multivariable logistic regression analysis

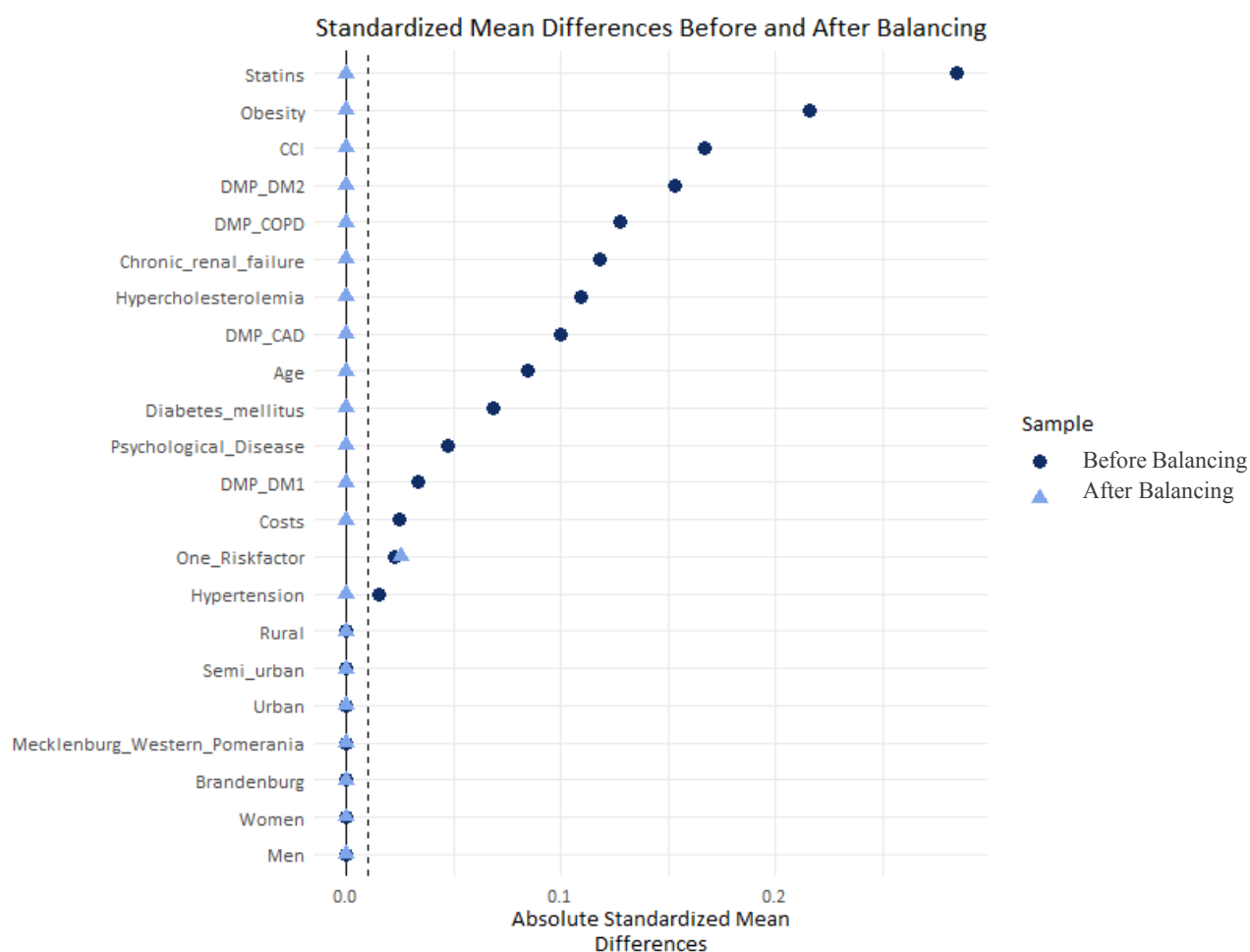
Results of the multivariable logistic regression analysis assessing the association of subclinical pre-heart failure with increasing age decades, sex, and individual cardiovascular risk factors. Results are given as OR with corresponding 95% CI.
CI = Confidence Interval, OR = Odds Ratio

Figure S5: Kaplan-Meier curves illustrating differences in HF-related event-free survival between participants with and without subclinical pre-HF

Please note that due to substantial interference of the intervention assessed in the integrated RCT, interpretability of differences is severely limited.



Kaplan-Meier curves showing a significant difference in the HF-free survival between HERZCHECK participants with and without subclinical pre-HF.
HF = Heart Failure

Figure S6: Comparison of the HERZCHECK subgroup and the control cohort before and after entropy balancing

Covariate balance plot showing that, according to the absolute standardized mean differences, the HERZCHECK subgroup and the historical control cohort were comparable after entropy balancing.

CCI = Charlson Comorbidity Index, DMP = Disease Management Program, CAD = Coronary Artery Disease, DM1 = Diabetes Mellitus Type 1, DM2 = Diabetes Mellitus Type 2, COPD = Chronic Obstructive Pulmonary Disease

3. Supplemental Tables

Table S1: Definition of covariates for matching and balancing of the control cohort

Variable	Characteristics		Baseline period		Definition/Comment
	Matching	Balancing	HERZCHECK participants	control cohort	
Sex	Female/male	Female/male	Year of CMR	2013	Last sex documented in claims data
Age	Age classes 40-44 45-49 50-54 55-59 60-64 65-70	Continuous (40-70*)	Day of CMR	31.12.2013	Truncated age
Region of residence Federal state Classification	BB/MVP urban/semi-urban/rural	BB/MVP urban/semi-urban/rural	Year of CMR [†]	2013	Last region documented in claims data
Risk factors [‡] Hypertension Diabetes mellitus Hypercholesterolemia Obesity Chronic kidney disease	At least one (yes/no)	Yes/no	12 months before CMR	2013	Inpatient main or secondary diagnosis or ≥ 2 secured outpatient diagnoses within two quarters in one year
Charlson comorbidity index ^{‡ 23,24}	-	Continuous (1-29)	12 months before CMR	2013	Inpatient main or secondary diagnosis or ≥ 1 secured outpatient diagnosis

Variable	Characteristics		Baseline period		Definition/Comment
	Matching	Balancing	HERZCHECK participants	control cohort	
Psychological disease ^l	-	Yes/no	12 months before CMR	2013	Inpatient main or secondary diagnosis or ≥ 1 secured outpatient diagnosis
Costs [‡]	-	Continuous	12 months before CMR	2013	Adjusted to 2023€
Statin intake	-	Yes/no	12 months before CMR	2013	Defined via ATC code C10AA
Participation in disease management program	-	Yes/no	Year of CMR [†]	2013	At least one documented enrollment
Diabetes mellitus 1					
Diabetes mellitus 2					
Coronary artery disease					
Chronic obstructive pulmonary disease					

* some participants were included in the study at age 69 years but turned 70 years before the first CMR; [†] no more detailed data was available; [‡] only diagnoses/costs of cases ending in the baseline period were considered; ^l selection criterion for study invitation letters from AOK Nordost

ATC = Anatomical Therapeutic Chemical (classification), BB = Brandenburg, CMR = Cardiac Magnetic Resonance, MVP = Mecklenburg-Western Pomerania

Table S2: Cross-table demonstrating the relationship between GLS-based subclinical pre-HF and normal or elevated NT-proBNP levels

N = 3,762	Elevated NT-proBNP (≥125 pg/mL)	Normal NT-proBNP (<125 pg/mL)	Total
Impaired GLS (≥ -15%)	281 (7.5%)	583 (15.5%)	864 (23.0%)
Preserved GLS (< -15%)	831 (22.1%)	2,067 (54.9%)	2,898 (77.0%)
Total	1,112 (29.6%)	2,650 (70.4%)	3,762 (100%)

GLS = Global Longitudinal Strain, HF = Heart Failure, NT-proBNP = N-terminal pro B-type natriuretic peptide

Table S3: Cross-table demonstrating the relationship between GLS-based subclinical pre-HF and preserved or reduced LVEF

N = 4,509	Reduced LVEF (<50%)	Preserved LVEF (≥50%)	Total
Impaired GLS (≥ -15%)	244 (5.4%)	779 (17.3%)	1,023 (22.7%)
Preserved GLS (< -15%)	45 (1.0%)	3,441 (76.3%)	3,486 (77.3%)
Total	289 (6.4%)	4,220 (93.6%)	100%

GLS = Global Longitudinal Strain, HF = Heart Failure, LVEF = Left Ventricular Ejection Fraction

Table S4: Results of adverse events in the HERZCHECK subgroup

	12 Months				
	Preserved (n=282)	GLS	Subclinical (n=842)	pre-HF	Total (n=1,124)
Mortality; n (%)	1 (0.35%)		10 (1.19%)		11 (0.98%)
HF-Hospitalization; n (%)	2 (0.71%)		41 (4.87%)		43 (3.83%)
	Preserved (n=221)	GLS	Subclinical (n=657)	pre-HF	Total (n=878)
HF; n (%)	6 (2.71%)		129 (19.63%)		135 (15.38%)

GLS = Global Longitudinal Strain, HF = Heart Failure

Table S5: Comparison of baseline characteristics between the HERZCHECK subgroup and the matched control cohort before entropy balancing

Variable	Total (n=9,262)	HERZ-CHECK participants (n=842)	Control Cohort (n=8,420)	ASMD
Age; mean [SD]	60.9 [7.2]	60.4 [7.1]	61.0 [7.2]	0.0834
≥60; n (%)	6,066 (65.5)	536 (63.7)	5,530 (65.6)	
Sex; n (%)				
Male	6,578 (71.0)	598 (71.0)	5,980 (71.0)	<0.0001
Female	2,684 (29.0)	244 (29.0)	2,440 (29.0)	<0.0001
Federal State; n (%)				
Mecklenburg-Western Pomerania	4,125 (44.5)	375 (44.5)	3,750 (44.5)	<0.0001
Brandenburg	5,137 (55.5)	467 (55.5)	4,670 (55.5)	<0.0001
Region; n (%)				
Urban	1,716 (18.5)	156 (18.5)	1,560 (18.5)	<0.0001
Semi-urban	3,960 (42.8)	360 (42.8)	3,600 (42.8)	<0.0001
Rural	3,586 (38.7)	326 (38.7)	3,260 (38.7)	<0.0001
Risk Factors; n (%)				
Hypertension	6,866 (74.1)	619 (73.5)	6,247 (74.2)	0.0154
Hypercholesterolemia	1,510 (16.3)	171 (20.3)	1,339 (15.9)	0.1146
Obesity	2,254 (24.3)	283 (33.6)	1,971 (23.4)	0.2274
Diabetes mellitus	3,098 (33.4)	307 (36.5)	2,791 (33.1)	0.0696
Renal insufficiency	560 (6.0)	77 (9.1)	483 (5.7)	0.1302
Number of risk factors; n (%)				
≥1	7,831 (84.5)	718 (85.3)	7,113 (84.5)	0.0222
1	3,506 (37.9)	262 (31.1)	3,244 (38.5)	
2	2,610 (28.2)	245 (29.1)	2,365 (28.1)	
3	1,323 (14.3)	149 (17.7)	1,174 (13.9)	
4	367 (4.0)	52 (6.2)	315 (3.7)	
5	25 (0.3)	10 (1.2)	15 (0.2)	
Psychological disease; n (%)	2,155 (23.3)	181 (21.5)	1,974 (23.4)	0.0467
Charlson comorbidity index; mean [SD]	1.7 [2.1]	2.1 [2.2]	1.7 [2.1]	0.1694
Statine intake; n (%)	2,399 (25.9)	324 (38.5)	2,075 (24.6)	0.3011
Disease Management Program; n (%)				
Diabetes mellitus Type 1	42 (0.5)	6 (0.7)	36 (0.4)	0.0379
Diabetes mellitus Type 2	2,047 (22.1)	239 (28.4)	1,808 (21.5)	0.1603
Coronary artery disease	604 (6.5)	77 (9.1)	527 (6.3)	0.1084
Chronic obstructive pulmonary disease	304 (3.3)	51 (6.1)	253 (3.0)	0.1472
Costs in €; mean [SD]	3,463.5 [8,794.6]	3,595.5 [5,917.9]	3,450.3 [9,032.2]	0.0190

ASMD = Absolute Standardized Mean Difference, CC = Control Cohort, SD = Standard Deviation

Table S6: Comparison of baseline characteristics between the HERZCHECK subgroup and the matched control cohort after entropy balancing

	Total (n=9,262)	HERZ-CHECK participants (n=842)	Control Cohort (n=8,420)	ASMD
Age; mean [SD]	60.4 [7.4]	60.4 [7.0]	60.4 [7.5]	<0.0001
≥ 60 years; n (%)	5,797 (62.6)	536 (63.7)	5,261 (62.5)	
Sex; n (%)				
Male	6,578 (71)	598 (71)	5,980 (71)	<0.0001
Female	2,684 (29)	244 (29)	2,440 (29)	<0.0001
Federal State; n (%)				
Mecklenburg-Western Pomerania	4,125 (55.5)	375 (55.5)	3,750 (55.5)	<0.0001
Brandenburg	5,137 (44.5)	467 (44.5)	4,670 (44.5)	<0.0001
Region; n (%)				
Rural	3,586 (38.7)	326 (38.7)	3,260 (38.7)	<0.0001
Semi-urban	3,960 (42.8)	360 (42.8)	3,600 (42.8)	<0.0001
Urban	1,716 (18.5)	156 (18.5)	1,560 (18.5)	<0.0001
Risk Factors; n (%)				
Hypertension	6,809 (73.5)	619 (73.5)	6,190 (73.5)	<0.0001
Hypercholesterolemia	1,881 (20.3)	171 (20.3)	1,710 (20.3)	<0.0001
Obesity	3,113 (33.6)	283 (33.6)	2,830 (33.6)	<0.0001
Diabetes mellitus	3,377 (36.5)	307 (36.5)	3,070 (36.5)	<0.0001
Renal insufficiency	847 (9.1)	77 (9.1)	770 (9.1)	<0.0001
Number of Risk Factors; n (%)				
≥1	7,975 (86.1)	718 (85.3)	7,257 (86.2)	0.0255
1	3,022 (32.6)	262 (31.1)	2,760 (32.8)	
2	2,580 (27.9)	245 (29.1)	2,335 (27.7)	
3	1,696 (18.3)	149 (17.7)	1,547 (18.4)	
4	629 (6.8)	52 (6.2)	577 (6.8)	
5	49 (0.5)	10 (1.2)	39 (0.5)	
Psychological disease; n (%)	1,991 (21.5)	181 (21.5)	1,810 (21.5)	<0.0001
Charlson comorbidity index; mean [SD]	2.1 [2.4]	2.1 [2.2]	2.1 [2.4]	<0.0001
Statine intake; n (%)	3,564 (38.5)	324 (38.5%)	3,240 (38.5)	<0.0001
Disease management program; n (%)				
Diabetes mellitus Type 1	66 (0.7)	6 (0.7)	60 (0.7)	<0.0001
Diabetes mellitus Type 2	2,629 (28.4)	239 (28.4)	2,390 (28.4)	<0.0001
Coronary artery disease	847 (9.1)	77 (9.1)	770 (9.1)	<0.0001
Chronic obstructive pulmonary disease	561 (6.1)	51 (6.1)	510 (6.1)	<0.0001
Costs in €; mean [SD]	3,595.5 [7,778.2]	3,595.5 [5,914.4]	3,595.5 [7,940.5]	<0.0001

ASMD = Absolute Standardized Mean Difference, SD = Standard Deviation

Table S7: Results of sensitivity and subgroup analyses for the time gained for prevention after entropy balancing

Scenario		Age; mean [SD]		Mean dif- ference; years	95% CI	p-value*
		HERZ- CHECK partici- pants	Control Cohort			
Base case						
Base case		60.9 [7.0]	67.5 [6.4]	6.7	6.11-7.25	<0.001
Sensitivity analyses†						
i) Diagnosis validation: validation of inpatient secondary diagnoses re- quired		60.9 [7.0]	67.8 [6.3]	7.0	6.30-7.55	<0.001
ii) Diagnosis validation: outpatient diagnoses must be in consecutive quarters		60.9 [7.0]	67.5 [6.4]	6.6	6.02-7.20	<0.001
iii) Balancing: including also cases ending after baseline period		60.9 [7.0]	67.5 [6.4]	6.7	6.04-7.25	<0.001
iv) Balancing: Rounded Age		60.9 [7.0]	67.9 [6.2]	7.0	6.42-7.56	<0.001
v) Balancing: only incident cases		60.9 [7.0]	65.1 [7.6]	4.2	3.54-4.96	<0.001
vi) Age at diagnosis: conservative calculation		60.9 [7.0]	67.5 [6.4]	6.6	6.01-7.13	<0.001
Subgroup analyses						
Sex	Male (n=6,578)	61.0 [7.2]	67.6 [6.4]	6.6	5.86–7.28	<0.001
	Female (n=2,684)	60.7 [6.7]	67.5 [6.3]	6.8	5.62–7.93	<0.001
Region	Urban (n=1,716)	60.0 [7.4]	68.2 [6.6]	8.2	6.85–9.64	<0.001
	Semi-urban (n=3,960)	60.9 [7.0]	67.4 [6.3]	6.4	5.50–7.35	<0.001
	Rural (n=3,586)	61.3 [6.9]	67.4 [6.4]	6.1	5.19–7.03	<0.001

* p-values were adjusted using Benjamini-Hochberg procedure, [†] refer to section methods S4 for methodological details, CI = Confidence Interval, HF = Heart Failure, SD = Standard Deviation

Table S8: Results of sensitivity and subgroup analyses for the HF incidence after entropy balancing

Scenario		Observation time; years (mean per patient)	Incidence; n (%)	Incidence rate (per 1000 patient years)	Overall mortality; n (%)	Mortality in incident cases; n (%)
Base case						
Base case		60,457.9 (7.2)	2,177 (25.9)	36.0	1,665 (19.8)	613 (30.6)
Sensitivity analyses						
i) Diagnosis validation: validation of inpatient secondary diagnoses required		63,288.0 (7.5)	1,449 (17.2)	22.9	1,665 (19.8)	359 (27.0)
ii) Diagnosis validation: outpatient diagnoses must be in consecutive quarters		60,577.0 (7.2)	2,149 (25.5)	35.5	1,665 (19.8)	610 (30.9)
Subgroup analyses						
Sex	Male (n=5,980)	42,192.9 (7.1)	1,646 (27.5)	39.0	1,315 (22.0)	516 (33.7)
	Female (n=2,440)	18,261.1 (7.5)	546 (22.4)	29.9	331 (13.6)	97 (20.4)
Region	Urban (n=1,560)	11,603.3 (7.4)	328 (21.0)	28.3	336 (21.5)	117 (36.8)
	Semi-urban (n=3,600)	25,692.6 (7.1)	983 (27.3)	38.2	694 (19.3)	258 (29.0)
	Rural (n=3,260)	23,155.6 (7.1)	867 (26.6)	37.4	628 (19.3)	238 (29.8)
Age	Age 40-49 (n=710)	6,015.5 (8.5)	49 (6.9)	8.1	42 (5.9)	13 (25.5)
	Age 50-59 (n=2,180)	16,900.5 (7.8)	376 (17.2)	22.2	299 (13.7)	82 (22.6)
	Age 60-70 (n=5,530)	37,601.5 (6.8)	1,734 (31.4)	46.1	1,328 (24.0)	518 (32.6)

HF = Heart Failure

Table S9: Results of sensitivity and subgroup analyses for the time gained for prevention before entropy balancing

Scenario		Age; mean [SD]		Mean dif- ference; years	95% CI	p-value*
		HERZ- CHECK partici- pants	Control Cohort			
Base case						
Base case		60.9 [7.0]	68.1 [6.1]	7.2	6.69-7.77	< 0.001
Sensitivity analyses [†]						
i) Diagnosis validation: validation of inpatient secondary diagnoses required		60.9 [7.0]	68.4 [6.1]	7.5	6.92-8.08	< 0.001
ii) Diagnosis validation: outpatient diagnoses must be in consecutive quarters		60.9 [7.0]	68.1 [6.1]	7.2	6.7-7.76	< 0.001
iii) Balancing: including also cases ending after baseline period		60.9 [7.0]	68.1 [6.1]	7.2	6.69-7.77	< 0.001
iv) Balancing: Rounded Age		60.9 [7.0]	68.1 [6.1]	7.2	6.69-7.77	< 0.001
v) Balancing: only incident cases		60.9 [7.0]	68.1 [6.1]	7.2	6.69-7.77	< 0.001
vi) Age at diagnosis: conservative calculation		60.9 [7.0]	68.1 [6.1]	7.2	6.63-7.71	< 0.001
Subgroup analyses						
Sex	Male (n=6,578)	61.0 [7.2]	68.1 [6.2]	7.1	6.51-7.81	< 0.001
	Female (n=2,684)	60.7 [6.7]	68.2 [6.0]	7.5	6.48-8.59	< 0.001
Region	Urban (n=1,716)	60.0 [7.4]	68.4 [6.5]	8.4	6.97-9.77	< 0.001
	Semi-urban (n=3,960)	60.9 [7.0]	68.2 [6.0]	7.2	6.41-8.02	< 0.001
	Rural (n=3,586)	61.3 [6.9]	67.9 [6.2]	6.7	5.84-7.58	< 0.001

* p-values were adjusted using Benjamini-Hochberg procedure, [†] refer to section Methods S4 for methodological details, CI = Confidence Interval, HF = Heart Failure, SD = Standard Deviation

Table S10: Results of sensitivity and subgroup analyses for the HF incidence before entropy balancing

Scenario		Observation time; years (mean per patient)	Incidence; n (%)	Incidence rate (per 1000 patient years)	Overall mortality; n (%)	Mortality in incident cases; n (%)
Base case						
Base case		61,344.4 (7.3)	2,005 (23.8)	32.7	1,654 (19.6)	613 (30.6)
Sensitivity analyses						
i) Diagnosis validation: validation of inpatient secondary diagnoses required		63,866.8 (7.6)	1,329 (15.8)	20.8	1,654 (19.6)	359 (27.0)
ii) Diagnosis validation: outpatient diagnoses must be in consecutive quarters		61,460.3 (7.3)	1,976 (23.5)	32.2	1,654 (19.6)	610 (30.9)
Subgroup analyses						
Sex	Male (n=5,980)	42,452.9 (7.1)	1,530 (25.6)	36.0	1,383 (23.1)	516 (33.7)
	Female (n=2,440)	18,891.5 (7.7)	1,976 (19.5)	25.1	271 (11.1)	97 (20.4)
Region	Urban (n=1,560)	11,540.1 (7.4)	318 (20.4)	27.6	349 (22.4)	117 (36.8)
	Semi-urban (n=3,600)	26,322.3 (7.3)	889 (24.7)	33.8	659 (18.3)	258 (29.0)
	Rural (n=3,260)	23,482.0 (7.2)	798 (24.5)	34.0	646 (19.8)	238 (29.8)
Age	Age 40-49 (n=710)	5,980.3 (8.4)	51 (7.2)	8.5	53 (7.5)	13 (25.5)
	Age 50-59 (n=2,180)	17,021.2 (7.8)	363 (16.7)	21.3	296 (13.6)	82 (22.6)
	Age 60-70 (n=5,530)	38,342.9 (6.9)	1,591 (28.8)	41.5	1,305 (23.6)	518 (32.6)

HF = Heart Failure

References

References are listed in the main manuscript (chapter 5.1).

Supplementary material to chapter 5.2 (DP II)

The supplementary material presented in this appendix has been previously published in 'Value Health' (2026, 29:1560-1570, doi:10.1016/j.jval.2026.04.002).

Cost-Effectiveness of a Global Longitudinal Strain-Based Screening and Prevention Program for Pre-Heart Failure Compared With Standard of Care: Supplementary material

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1. Characteristics of HERZCHECK participants with pre-HF

Table 1: Participants' characteristics

HERZCHECK participants with pre-HF (n=1,023)	
Demographics	
Sex ^a	
male	732 (72%)
female	291 (28%)
Age (years)	60 ± 7
CMR and laboratory	
GLS (%)	-14.37 [-15.02 – -13.33]
LVEF (%)	53.69 ± 6.98
NT-proBNP (pmol/l)	23.98 ± 60.36 ^b
Risk factors	
Diabetes mellitus Type 2	316 (31%) ^c
Renal failure	42 (4%) ^c
Hypertension	782 (77%) ^c
Hypercholesterolemia	486 (48%) ^c
Obesity	530 (52%)
Smoking	698 (68%) ^c
Cardiovascular history	
CAD	112 (11%) ^d
MI	69 (7%) ^c
Arrhythmia	130 (13%) ^d

Data are presented as mean ± standard deviation, median [interquartile range], or n (%)

^a self-reported biological sex, ^b missings = 159, ^c missings = 2, ^d missings = 30, ^e missings = 27

CAD = Coronary Artery Disease, CMR = Cardiac Magnetic Resonance, GLS = Global Longitudinal Strain, HF = Heart Failure, LVEF = Left Ventricular Ejection Fraction, MI = Myocardial Infarction, NT-proBNP = N-terminal prohormone of Brain Natriuretic Peptide

2. Details on input parameters

Adequate literature was identified via systematic literature searches in scientific databases (e.g. PubMed) and by searching for reference lists and grey literature¹. Study selection was guided by methodological study quality and the studies' representativeness for the context of this analysis.

Using a patient-level simulation model, transition probabilities were based on patient characteristics (e.g. age, sex) and patient history (e.g. number of HF hospitalizations).

Table 2: Clinical input parameters

Parameter		Value (per month)	Distribution ^a	Range ^b	Source
pre-HF prevalence		0.2268	Beta ($\alpha = 1023$, $\beta = 3486$)	95% CI: 0.2146 – 0.2391	²
Background mortality (pre-HF women)	Age 40-<45 years	6.0165E-05	PERT (mode ^c , 95% CI)	95% CI: 9.3424E-07 – 3.8601E-03	³
	Age 45-<50 years	9.6579E-05	PERT (mode ^c , 95% CI)	95% CI: 2.3638E-06 – 3.9313E-03	
	Age 50-<55 years	1.5990E-04	PERT (mode ^c , 95% CI)	95% CI: 6.2843E-06 – 4.0535E-03	
	Age 55-<60 years	2.5747E-04	PERT (mode ^c , 95% CI)	95% CI: 1.5581E-05 – 4.2386E-03	
	Age 60-<65 years	4.2791E-04	PERT (mode ^c , 95% CI)	95% CI: 4.0060E-05 – 4.5537E-03	
	Age 65-<70 years	6.8235E-04	PERT (mode ^c , 95% CI)	95% CI: 9.2621E-05 – 5.0082E-03	
	Age 70-<75 years	1.0196E-03	PERT (mode ^c , 95% CI)	95% CI: 1.8535E-04 – 5.5873E-03	
	Age 75-<80 years	1.6174E-03	PERT (mode ^c , 95% CI)	95% CI: 3.9684E-04 – 6.5669E-03	
	Age 80-<85 years	2.6684E-03	PERT (mode ^c , 95% CI)	95% CI: 8.6590E-04 – 8.1920E-03	
	Age 85-<90 years	4.7333E-03	PERT (mode ^c , 95% CI)	95% CI: 1.9973E-03 – 1.1175E-02	
	Age ≥ 90 years	1.0102E-02	PERT (mode ^c , 95% CI)	95% CI: 5.5498E-03 – 1.8320E-02	
Background mortality (pre-HF men)	Age 40-<45 years	1.0808E-04	PERT (mode ^c , 95% CI)	95% CI: 2.9434E-06 – 3.9536E-03	³
	Age 45-<50 years	1.6015E-04	PERT (mode ^c , 95% CI)	95% CI: 6.3033E-06 – 4.0540E-03	
	Age 50-<55 years	2.6463E-04	PERT (mode ^c , 95% CI)	95% CI: 1.6408E-05 – 4.2521E-03	
	Age 55-<60 years	4.2941E-04	PERT (mode ^c , 95% CI)	95% CI: 4.0317E-05 – 4.5565E-03	
	Age 60-<65 years	7.2657E-04	PERT (mode ^c , 95% CI)	95% CI: 1.0342E-04 – 5.0855E-03	
	Age 65-<70 years	1.1421E-03	PERT (mode ^c , 95% CI)	95% CI: 2.2434E-04 – 5.7925E-03	
	Age 70-<75 years	1.6919E-03	PERT (mode ^c , 95% CI)	95% CI: 4.2655E-04 – 6.6858E-03	
	Age 75-<80 years	2.5359E-03	PERT (mode ^c , 95% CI)	95% CI: 8.0162E-04 – 7.9925E-03	

Parameter		Value (per month)	Distribution ^a	Range ^b	Source
	Age 80-<85 years	4.0068E-03	PERT (mode ^c , 95% CI)	95% CI: 1.5760E-03 – 1.0149E-02	
	Age 85-<90 years	6.5370E-03	PERT (mode ^c , 95% CI)	95% CI: 3.1197E-03 – 1.3647E-02	
	Age ≥90 years	1.2314E-02	PERT (mode ^c , 95% CI)	95% CI: 7.1506E-03 – 2.1126E-02	
CV mortality (pre-HF women)	HR per 1% GLS increase	1.03			4
	GLS = -17.8%	0.0005	PERT (mode ^c , 95% CI)	95% CI: 0.0001 – 0.0047	
	GLS = -16.8%	0.0005	PERT (mode ^c , 95% CI)	95% CI: 0.0001 – 0.0047	
	GLS = -15.8%	0.0005	PERT (mode ^c , 95% CI)	95% CI: 0.0001 – 0.0047	
	GLS = -14.8%	0.0005	PERT (mode ^c , 95% CI)	95% CI: 0.0001 – 0.0047	
	GLS = -13.8%	0.0005	PERT (mode ^c , 95% CI)	95% CI: 0.0001 – 0.0048	
	GLS = -12.8%	0.0006	PERT (mode ^c , 95% CI)	95% CI: 0.0001 – 0.0048	
	GLS = -11.8%	0.0006	PERT (mode ^c , 95% CI)	95% CI: 0.0001 – 0.0048	
	GLS = -10.8%	0.0006	PERT (mode ^c , 95% CI)	95% CI: 0.0001 – 0.0049	
	GLS = -9.8%	0.0006	PERT (mode ^c , 95% CI)	95% CI: 0.0001 – 0.0049	
	GLS = -8.8%	0.0006	PERT (mode ^c , 95% CI)	95% CI: 0.0001 – 0.0049	
	GLS = -7.8%	0.0007	PERT (mode ^c , 95% CI)	95% CI: 0.0001 – 0.0050	
	GLS = -6.8%	0.0007	PERT (mode ^c , 95% CI)	95% CI: 0.0001 – 0.0050	
	GLS = -5.8%	0.0007	PERT (mode ^c , 95% CI)	95% CI: 0.0001 – 0.0050	
	GLS = -4.8%	0.0007	PERT (mode ^c , 95% CI)	95% CI: 0.0001 – 0.0051	
	GLS = -3.8%	0.0007	PERT (mode ^c , 95% CI)	95% CI: 0.0001 – 0.0051	
	GLS = -2.8%	0.0008	PERT (mode ^c , 95% CI)	95% CI: 0.0001 – 0.0051	
CV mortality (pre-HF men)	HR per 1% GLS increase	1.11			4
	GLS = -17.8%	0.0004	PERT (mode ^c , 95% CI)	95% CI: 0.0000-0.0044	
	GLS = -16.8%	0.0004	PERT (mode ^c , 95% CI)	95% CI: 0.0000-0.0045	
	GLS = -15.8%	0.0004	PERT (mode ^c , 95% CI)	95% CI: 0.0000-0.0046	
	GLS = -14.8%	0.0005	PERT (mode ^c , 95% CI)	95% CI: 0.0001-0.0047	
	GLS = -13.8%	0.0005	PERT (mode ^c , 95% CI)	95% CI: 0.0001-0.0048	
	GLS = -12.8%	0.0006	PERT (mode ^c , 95% CI)	95% CI: 0.0001-0.0049	
	GLS = -11.8%	0.0007	PERT (mode ^c , 95% CI)	95% CI: 0.0001-0.0050	
	GLS = -10.8%	0.0007	PERT (mode ^c , 95% CI)	95% CI: 0.0001-0.0051	
	GLS = -9.8%	0.0008	PERT (mode ^c , 95% CI)	95% CI: 0.0001-0.0052	

Parameter			Value (per month)	Distribution ^a	Range ^b	Source
	GLS = -8.8%		0.0009	PERT (mode ^c , 95% CI)	95% CI: 0.0002-0.0054	
	GLS = -7.8%		0.0010	PERT (mode ^c , 95% CI)	95% CI: 0.0002-0.0056	
	GLS = -6.8%		0.0011	PERT (mode ^c , 95% CI)	95% CI: 0.0002-0.0058	
	GLS = -5.8%		0.0012	PERT (mode ^c , 95% CI)	95% CI: 0.0003-0.0060	
	GLS = -4.8%		0.0014	PERT (mode ^c , 95% CI)	95% CI: 0.0003-0.0062	
	GLS = -3.8%		0.0015	PERT (mode ^c , 95% CI)	95% CI: 0.0004-0.0064	
	GLS = -2.8%		0.0017	PERT (mode ^c , 95% CI)	95% CI: 0.0004-0.0067	
Age-dependent CV mortality (pre-HF women)	HR per 5-year age class ^d		1.60			3
	HR vs. Age 60-<65 years	Age 40 - <45	0.15	PERT (mode ^c , ±10%)	±10%	
		Age 45 - <50	0.25	PERT (mode ^c , ±10%)	±10%	
		Age 50 - <55	0.39	PERT (mode ^c , ±10%)	±10%	
		Age 55 - <60	0.63	PERT (mode ^c , ±10%)	±10%	
		Age 60 - <65	1.00	PERT (mode ^c , ±10%)	±10%	
		Age 65 - <70	1.60	PERT (mode ^c , ±10%)	±10%	
		Age 70 - <75	2.55	PERT (mode ^c , ±10%)	±10%	
		Age 75 - <80	4.08	PERT (mode ^c , ±10%)	±10%	
		Age 80 - <85	6.52	PERT (mode ^c , ±10%)	±10%	
		Age 85 - <90	10.42	PERT (mode ^c , ±10%)	±10%	
		Age 90 +	16.66	PERT (mode ^c , ±10%)	±10%	
Age-dependent CV mortality (pre-HF men)	HR per 5-year age class ^d		1.57			3
	HR vs. Age 60-<65 years	Age 40 - <45	0.17	PERT (mode ^c , ±10%)	±10%	
		Age 45 - <50	0.26	PERT (mode ^c , ±10%)	±10%	
		Age 50 - <55	0.41	PERT (mode ^c , ±10%)	±10%	
		Age 55 - <60	0.64	PERT (mode ^c , ±10%)	±10%	
		Age 60 - <65	1.00	PERT (mode ^c , ±10%)	±10%	
		Age 65 - <70	1.57	PERT (mode ^c , ±10%)	±10%	
		Age 70 - <75	2.45	PERT (mode ^c , ±10%)	±10%	
		Age 75 - <80	3.84	PERT (mode ^c , ±10%)	±10%	
		Age 80 - <85	6.01	PERT (mode ^c , ±10%)	±10%	
		Age 85 - <90	9.42	PERT (mode ^c , ±10%)	±10%	

Parameter			Value (per month)	Distribution ^a	Range ^b	Source
Age 90 +			14.75	PERT (mode ^c , ±10%)	±10%	
All-cause mortality without prior HFH (symptomatic HF)	Month of HF diagnosis		0.0700	PERT (mode ^c , 95% CI)	95% CI: 0.0559 – 0.0873	5
	1 month - 11 months after HF diagnosis		0.0118	PERT (mode ^c , 95% CI)	95% CI: 0.0067 – 0.0204	
	≥12 months after HF diagnosis		0.0100	PERT (mode ^c , 95% CI)	95% CI: 0.0054 – 0.0181	
All-cause mortality with 1 prior HFH (symptomatic HF)	Month of the HFH		0.1319	PERT (mode ^c , 95% CI)	95% CI: 0.1126 – 0.1541	6, log-logistic curve ^e
	1 month after HFH		0.0405	PERT (mode ^c , 95% CI)	95% CI: 0.0300 – 0.0543	
	2 months after HFH		0.0286	PERT (mode ^c , 95% CI)	95% CI: 0.0200 – 0.0407	
	3 months after HFH		0.0227	PERT (mode ^c , 95% CI)	95% CI: 0.0152 – 0.0338	
	4 months after HFH		0.0192	PERT (mode ^c , 95% CI)	95% CI: 0.0124 – 0.0295	
	5 months after HFH		0.0167	PERT (mode ^c , 95% CI)	95% CI: 0.0105 – 0.0265	
	6 months after HFH		0.0149	PERT (mode ^c , 95% CI)	95% CI: 0.0091 – 0.0243	
	7 months after HFH		0.0135	PERT (mode ^c , 95% CI)	95% CI: 0.0080 – 0.0226	
	8 months after HFH		0.0123	PERT (mode ^c , 95% CI)	95% CI: 0.0072 – 0.0212	
	9 months after HFH		0.0114	PERT (mode ^c , 95% CI)	95% CI: 0.0065 – 0.0200	
	10 months after HFH		0.0106	PERT (mode ^c , 95% CI)	95% CI: 0.0059 – 0.0190	
	11 months after HFH		0.0100	PERT (mode ^c , 95% CI)	95% CI: 0.0054 – 0.0181	
	≥12 months after HFH ^f		0.0075	PERT (mode ^c , 95% CI)	95% CI: 0.0038 – 0.0150	
HF progression (symptomatic HF)	HR per HFH on mortality		1.33	lognormal (mean of log = 0.2883, SD of log = 0.0137)	95% CI: 1.31 – 1.35	7
Age-dependent mortality (HF women)	HR per 5-year age class ^d		1.38			3
	HR vs. Age 75-<70 years	Age 40 - <45	0.1026	PERT (mode ^c , ±10%)	±10%	
		Age 45 - <50	0.1420	PERT (mode ^c , ±10%)	±10%	
		Age 50 - <55	0.1966	PERT (mode ^c , ±10%)	±10%	
		Age 55 - <60	0.2722	PERT (mode ^c , ±10%)	±10%	
		Age 60 - <65	0.3769	PERT (mode ^c , ±10%)	±10%	
		Age 65 - <70	0.5218	PERT (mode ^c , ±10%)	±10%	
		Age 70 - <75	0.7223	PERT (mode ^c , ±10%)	±10%	
		Age 75 - <80	1.0000	PERT (mode ^c , ±10%)	±10%	
		Age 80 - <85	1.3844	PERT (mode ^c , ±10%)	±10%	
		Age 85 - <90	1.9166	PERT (mode ^c , ±10%)	±10%	

Parameter			Value (per month)	Distribution ^a	Range ^b	Source
Age 90 +			2.6533	PERT (mode ^c , ±10%)	±10%	
Age-dependent mortality (HF men)	HR per 5-year age class ^d		1.44			3
	HR vs. Age 75-<70 years	Age 40 - <45	0.0795	PERT (mode ^c , ±10%)	±10%	
		Age 45 - <50	0.1141	PERT (mode ^c , ±10%)	±10%	
		Age 50 - <55	0.1639	PERT (mode ^c , ±10%)	±10%	
		Age 55 - <60	0.2353	PERT (mode ^c , ±10%)	±10%	
		Age 60 - <65	0.3378	PERT (mode ^c , ±10%)	±10%	
		Age 65 - <70	0.4851	PERT (mode ^c , ±10%)	±10%	
		Age 70 - <75	0.6965	PERT (mode ^c , ±10%)	±10%	
		Age 75 - <80	1.0000	PERT (mode ^c , ±10%)	±10%	
		Age 80 - <85	1.4358	PERT (mode ^c , ±10%)	±10%	
		Age 85 - <90	2.0615	PERT (mode ^c , ±10%)	±10%	
		Age 90 +	2.9599	PERT (mode ^c , ±10%)	±10%	
HF incidence (women)	HR per 1% GLS increase		1.09			4
	GLS = -17.8%		0.0004	PERT (mode ^c , 95% CI)	95% CI: 0.0000-0.0046	
	GLS = -16.8%		0.0005	PERT (mode ^c , 95% CI)	95% CI: 0.0001-0.0047	
	GLS = -15.8%		0.0005	PERT (mode ^c , 95% CI)	95% CI: 0.0001-0.0047	
	GLS = -14.8%		0.0006	PERT (mode ^c , 95% CI)	95% CI: 0.0001-0.0048	
	GLS = -13.8%		0.0006	PERT (mode ^c , 95% CI)	95% CI: 0.0001-0.0049	
	GLS = -12.8%		0.0007	PERT (mode ^c , 95% CI)	95% CI: 0.0001-0.0050	
	GLS = -11.8%		0.0007	PERT (mode ^c , 95% CI)	95% CI: 0.0001-0.0051	
	GLS = -10.8%		0.0008	PERT (mode ^c , 95% CI)	95% CI: 0.0001-0.0052	
	GLS = -9.8%		0.0009	PERT (mode ^c , 95% CI)	95% CI: 0.0001-0.0054	
	GLS = -8.8%		0.0010	PERT (mode ^c , 95% CI)	95% CI: 0.0002-0.0055	
	GLS = -7.8%		0.0011	PERT (mode ^c , 95% CI)	95% CI: 0.0002-0.0057	
	GLS = -6.8%		0.0012	PERT (mode ^c , 95% CI)	95% CI: 0.0002-0.0058	
	GLS = -5.8%		0.0013	PERT (mode ^c , 95% CI)	95% CI: 0.0003-0.0060	
	GLS = -4.8%		0.0014	PERT (mode ^c , 95% CI)	95% CI: 0.0003-0.0062	
	GLS = -3.8%		0.0015	PERT (mode ^c , 95% CI)	95% CI: 0.0003-0.0064	
	GLS = -2.8%		0.0016	PERT (mode ^c , 95% CI)	95% CI: 0.0004-0.0066	

Parameter			Value (per month)	Distribution ^a	Range ^b	Source
HF incidence (men)	HR per 1% GLS increase		1.22			4
	GLS = -17.8%		0.0004	PERT (mode ^c , 95% CI)	95% CI: 0.0000-0.0046	
	GLS = -16.8%		0.0005	PERT (mode ^c , 95% CI)	95% CI: 0.0001-0.0047	
	GLS = -15.8%		0.0006	PERT (mode ^c , 95% CI)	95% CI: 0.0001-0.0049	
	GLS = -14.8%		0.0008	PERT (mode ^c , 95% CI)	95% CI: 0.0001-0.0052	
	GLS = -13.8%		0.0010	PERT (mode ^c , 95% CI)	95% CI: 0.0002-0.0055	
	GLS = -12.8%		0.0012	PERT (mode ^c , 95% CI)	95% CI: 0.0002-0.0058	
	GLS = -11.8%		0.0014	PERT (mode ^c , 95% CI)	95% CI: 0.0003-0.0062	
	GLS = -10.8%		0.0017	PERT (mode ^c , 95% CI)	95% CI: 0.0004-0.0067	
	GLS = -9.8%		0.0021	PERT (mode ^c , 95% CI)	95% CI: 0.0006-0.0073	
	GLS = -8.8%		0.0026	PERT (mode ^c , 95% CI)	95% CI: 0.0008-0.0080	
	GLS = -7.8%		0.0031	PERT (mode ^c , 95% CI)	95% CI: 0.0011-0.0089	
	GLS = -6.8%		0.0038	PERT (mode ^c , 95% CI)	95% CI: 0.0015-0.0099	
	GLS = -5.8%		0.0047	PERT (mode ^c , 95% CI)	95% CI: 0.0020-0.0111	
	GLS = -4.8%		0.0057	PERT (mode ^c , 95% CI)	95% CI: 0.0026-0.0125	
	GLS = -3.8%		0.0069	PERT (mode ^c , 95% CI)	95% CI: 0.0034-0.0142	
	GLS = -2.8%		0.0084	PERT (mode ^c , 95% CI)	95% CI: 0.0044-0.0162	
Age-dependent HF incidence	HR vs. Age 60-<65 years ^d	Age 40 - <45	0.82	PERT (mode ^c , ±10%)	±10%	Assumption
		Age 45 - <50	0.86	PERT (mode ^c , ±10%)	±10%	
		Age 50 - <55	0.91	PERT (mode ^c , ±10%)	±10%	
		Age 55 - <60	0.95	PERT (mode ^c , ±10%)	±10% ^e	
		Age 60 - <65	1.00	PERT (mode ^c , ±10%)	±10%	
		Age 65 - <70	1.05	PERT (mode ^c , ±10%)	±10% ^e	
		Age 70 - <75	1.10	PERT (mode ^c , ±10%)	±10%	
		Age 75 - <80	1.16	PERT (mode ^c , ±10%)	±10%	
		Age 80 - <85	1.22	PERT (mode ^c , ±10%)	±10%	
		Age 85 - <90	1.28	PERT (mode ^c , ±10%)	±10%	
		Age 90 +	1.34	PERT (mode ^c , ±10%)	±10%	

Parameter			Value (per month)	Distribution ^a	Range ^b	Source
Proportion of inpatient diagnoses			0.5980	Beta ($\alpha = 1199$, $\beta = 806$)	95% CI: 0.5776 – 0.6180	HER-ZCK
HFH	1. hospitalization (symptomatic HF)	<12 months after diagnosis	0.0102	PERT (mode ^c , 95% CI)	95% CI: 0.0056 – 0.0184	5
		≥12 months after diagnosis	0.0054	PERT (mode ^c , 95% CI)	95% CI: 0.0024 – 0.0121	
	Rehospitalization after 1 HFH (symptomatic HF)	Month of the HFH	0.0418	PERT (mode ^c , 95% CI)	95% CI: 0.0312 – 0.0559	6, log-normal curve ^h
		1 month after HFH	0.0248	PERT (mode ^c , 95% CI)	95% CI: 0.0169 – 0.0362	
		2 months after HFH	0.0194	PERT (mode ^c , 95% CI)	95% CI: 0.0125 – 0.0298	
		3 months after HFH	0.0163	PERT (mode ^c , 95% CI)	95% CI: 0.0102 – 0.0261	
		4 months after HFH	0.0143	PERT (mode ^c , 95% CI)	95% CI: 0.0086 – 0.0236	
		5 months after HFH	0.0128	PERT (mode ^c , 95% CI)	95% CI: 0.0075 – 0.0218	
		6 months after HFH	0.0117	PERT (mode ^c , 95% CI)	95% CI: 0.0067 – 0.0203	
		7 months after HFH	0.0108	PERT (mode ^c , 95% CI)	95% CI: 0.0060 – 0.0192	
		8 months after HFH	0.0100	PERT (mode ^c , 95% CI)	95% CI: 0.0055 – 0.0182	
		9 months after HFH	0.0094	PERT (mode ^c , 95% CI)	95% CI: 0.0051 – 0.0174	
		10 months after HFH	0.0089	PERT (mode ^c , 95% CI)	95% CI: 0.0047 – 0.0167	
		11 months after HFH	0.0084	PERT (mode ^c , 95% CI)	95% CI: 0.0044 – 0.0161	
		≥12 months after HFH ^f	0.0066	PERT (mode ^c , 95% CI)	95% CI: 0.0032 – 0.0137	
	HR per HFH on risk of HFH		1.25	lognormal (mean of log = 0.2192, SD of log = 0.0087)	95% CI: 1.23-1.26	7
Intervention effect	HR HF incidence (screening arm)		0.80	lognormal (mean of log = -0.2231, SD of log = 0.0448)	95% CI: 0.73 – 0.87	8
	HR mortality (screening arm)		0.89	lognormal (mean of log = -0.1165, SD of log = 0.1140)	95% CI: 0.71 – 1.11	

^a probabilistic sensitivity analysis, ^b deterministic sensitivity analysis (all clinical parameters were varied by their 95% confidence limits or, in the absence of information, by $\pm 10\%$), ^c the reported mean value was used as proxy for the mode of the PERT distribution, ^d mortality was fitted to reach that of the general German population at age ≥ 90 years³. HF incidence was then adjusted taking into account an expected loss of life due to HF of about 2 years⁹, ^e shape = 0.4000478, scale = 9.24887996. Data were calibrated to a log-logistic curve, with distribution parameters estimated by solving nonlinear equations (multiroot function, R package rootSolve^{10,11}) based on observed survival probabilities at specific time points, ^f based on a one-year period (2nd year after HFH), ^g adjustment for 95% CI of age 55 - <59 and age 65 - <69 so that the upper or lower limit = 1, ^h mean = 2.959508, SD = 3.146984. Data were calibrated to a log-normal curve, with distribution parameters estimated by solving nonlinear equations (multiroot function, R package rootSolve^{10,11}) based on observed survival probabilities at specific time points

CI = Confidence Interval, CV = Cardiovascular, GLS = Global Longitudinal Strain, HF = Heart Failure, HFH = Heart Failure Hospitalization, HR = Hazard Ratio, SD = Standard Deviation

Table 3: Costs, utilities, and discount rate

Parameter	Value	Distribution ^a	Range ^b	Source
<i>Costs (€/month per patient)</i>				
One-time screening per screened individual ^c (screening arm)	672.00	PERT (mode ^d , min = 482.00, max = 712.00)	482.00 – 712.00	HERZCHECK
Intervention (screening arm)	33.31 ^e	Gamma (mean, SD = 3.40)	±20%	12,13
Pre-HF (screening arm)	24.05	PERT (mode ^d , 95% CI)	95% CI: 0.00 – 73.50	HERZCHECK
HF without hospitalization ^f	without rehabilitation costs (age <67 years)	Gamma (mean, SD = 2.46)	95% CI: 53.04 – 62.68	HERZCHECK
	with rehabilitation costs (age ≥ 67 years)	Gamma (mean, SD = 2.83)	95% CI: 83.23 – 94.32	14,15
HFH	8,778.58	Gamma (mean, SD = 316.15)	95% CI: 8,158.93 – 9,398.23	HERZCHECK
<i>Utilities</i>				
Pre-HF	0.813	Beta (mean, SD = 0.007)	95% CI: 0.802 – 0.828	HERZCHECK, 16
HF without hospitalization	0.730	Beta (mean, SD = 0.008)	95% CI: 0.715 – 0.745	17
Disutility of HFH	≤30 days after HFH	Beta (mean, SD = 0.006)	95% CI: 0.093 – 0.117	18
	30-90 days after HFH	Beta (mean, SD = 0.004)	95% CI: 0.046 – 0.062	18
<i>Discount rate (per year)</i>				
Costs and effects	0.03	-	0.00 – 0.05	19

^a probabilistic sensitivity analysis, ^b deterministic sensitivity analysis (all cost parameters were varied by their 95% confidence limits or, in the absence of information, by ± 20%), ^c costs per detected pre-HF patient were implemented in the model as *costs per screened individual/pre-HF prevalence*, ^d the reported mean value was used as proxy for the mode of the PERT distribution, ^e see Table 5 for calculation, ^f cardiovascular main diagnosis with heart failure as main or secondary diagnosis

CI = Confidence Interval, HF = Heart Failure, HFH = Heart Failure Hospitalization, SD = Standard Deviation

Table 4: Input parameters for sensitivity and scenario analyses

Parameter		Value (per month)	Source
(Non-HF) costs of added LYs (women)	Age 30-<45 years	€295.40	20,21
	Age 45-<65 years	€441.08	
	Age 65-<85 years	€945.57	
	Age ≥85 years	€2,496.34	
(Non-HF) costs of added LYs (men)	Age 30-<45 years	€204.74	
	Age 45-<65 years	€424.46	
	Age 65-<85 years	€986.71	
	Age ≥85 years	€2,040.45	
Mortality at age ≥90 years (women)		0.0197	3
Mortality at age ≥90 years (men)		0.0220	
Incidence at age ≥90 years (women)		0.0038	22
Incidence at age ≥90 years (men)		0.0043	

HF = Heart Failure, LY = Life Year

Table 5: Resource use and prices

Resource	Frequency (per year)	Price	Costs (per year)	Costs (per month)	Source
<i>Outpatient care^a</i>					
Rehabilitation	0.1	€3,709.67		€30.91	14,15
<i>Intervention</i>					
Counselling on diet					
Individual session (anamnesis)	1	€66.50	€66.50		13
Group session	4	€23.27	€93.08		13
Overall (diet)			€159.58	€13.30	
Counselling on physical activity					
Individual session	4	€24.07	€96.28		12
Group session	21	€6.85	€143.85		12
Overall (physical activity)			€240.13	€20.01	
Overall			€399.71	€33.31	

^a Note that other costs (e.g., costs of outpatient physician care) were obtained from the claims data set.

Table 6: Trends for option value

Input parameter	Trend	Source
HF Incidence	$-0.00008 * \text{LN}((132^a + \text{cycle})/12) + (\text{prob} + 0.00008 * \text{LN}(132^a/12))$	23
Mortality (pre-HF patients)		24
Age <65 years	$-0.00001 * \text{LN}((312^b + \text{cycle})/12) + (\text{prob} + 0.00001 * \text{LN}(312^b/12))$	
Age 65-<80 years	$-0.0002 * \text{LN}((312^b + \text{cycle})/12) + (\text{prob} + 0.0002 * \text{LN}(312^b/12))$	
Age ≥80 years	$-0.0008 * \text{LN}((312^b + \text{cycle})/12) + (\text{prob} + 0.0008 * \text{LN}(312^b/12))$	
Mortality (HF patients)		3
Age <65 years	$-0.002 * \text{LN}((336^c + \text{cycle})/12) + (\text{prob} + 0.002 * \text{LN}(336^c/12))$	
Age 65-<80 years	$-0.004 * \text{LN}((336^c + \text{cycle})/12) + (\text{prob} + 0.004 * \text{LN}(336^c/12))$	
Age ≥80 years	$-0.004 * \text{LN}((336^c + \text{cycle})/12) + (\text{prob} + 0.004 * \text{LN}(336^c/12))$	
Costs	$\text{costs} * (1.0585971781282641)^{(\text{cycle}/12)}$	25

HF = Heart Failure, prob = probability, LN = natural logarithm

^a Trends were based on data from 2013 to 2021, ^b Trends were based on data from 1998 to 2023, ^c Trends were based on data from 1996 to 2020

3. HRQoL-Mapping

Regression analysis for estimating EQ-5D-5L preference-based health index scores from PRO-MIS-29 profile for Germany¹⁶:

$$\begin{aligned}
 EQ - 5D = & -1.181 + 0,007425 * \text{T-Score "depression"} + 0,08834 \\
 & * \text{T-Score "participation"} + 0,0005596 \\
 & * (\text{T-Score "physical function"}^2) - 0,00001763 \\
 & * (\text{T-Score "sleep disturbance"}^2) - 0,001733 \\
 & * (\text{T-Score "ability to participate in social roles and activities"}^2) \\
 & - 0,000000148 * (\text{T-Score "anxiety"}^3) - 0,0000008951 \\
 & * (\text{T-Score "depression"}^3) - 0,0000007808 \\
 & * (\text{T-Score "pain interference"}^3) - 0,000006865 \\
 & * (\text{T-Score "physical function"}^3) + 0,00001113 \\
 & * (\text{T-Score "ability to participate in social roles and activities"}^3)
 \end{aligned}$$

4. Details on the intervention

To reflect the resource use for preventive measures, a lifestyle intervention provided for three consecutive 4-month phases was assumed⁸. In accordance to studies included in the systematic review used for the effect⁸, several estimates were estimated:

- i) weekly sessions (1 individual nutritional counselling + 2 group counselling sessions, 2 individual exercise therapies + 13 group therapies)
- ii) biweekly sessions (1 group counselling, 1 individual exercise therapy + 6 group therapies)
- iii) monthly sessions (1 group counselling, 1 individual exercise therapy + 2 group therapies)

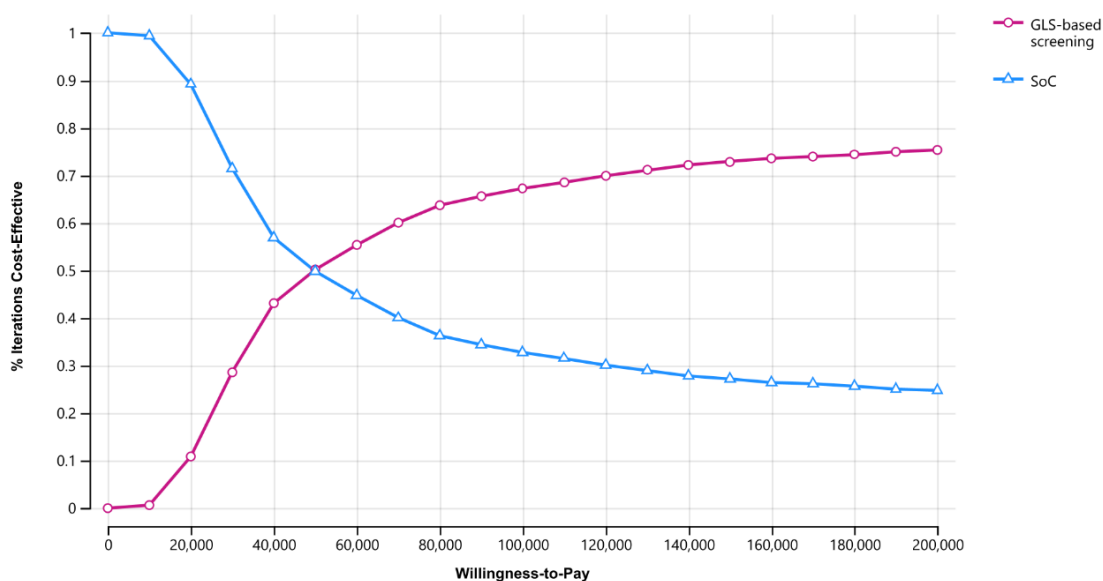
5. Results of PSA

Table 7: Results of PSA

	Costs (€)	Incre- mental Costs (€)	Effectiveness		Incremental Effectiveness		ICER	
			QALY	LY	QALY	LY	€/QALY	€/LY
PSA								
SoC	3,365.98		10.05	12.54				
HERZ-CHECK	10,219.42	6,852.44	10.18	12.69	0.13	0.15	51,125.96	44,768.18

ICER = Incremental Cost-Effectiveness Ratio, LY = Life Year, PSA = Probabilistic Sensitivity Analysis, QALY = Quality Adjusted Life Year, SoC = Standard of Care

Figure 1: Cost-effectiveness-acceptability curve



GLS = Global Longitudinal Strain, SoC = Standard of Care

6. Results of the option value model

Table 8: Results of option value model

	Costs (€)	Incremen- tal Costs (€)	Effectiveness		Incremental Effectiveness		ICER	
			QALY	LY	QALY	LY	€/QALY	€/LY
OV model								
SoC	5,786.85		11.38	14.14				
HERZ- CHECK	16,975.94	11,189.09	11.48	14.25	0.10	0.12	110,854.32	95,472.78

ICER = Incremental Cost-Effectiveness Ratio, LY = Life Year, OV = Option Value, QALY = Quality Adjusted Life Year, SoC = Standard of Care

7. Details on validation

According to: Assessment of the Validation Status of Health-Economic decision models (AdViSHE)²⁶

Part A: Validation of the conceptual model

A1/Face validity testing (conceptual model):

Have experts been asked to judge the appropriateness of the conceptual model?

Prof. Dr. med. SK (cardiologist), Prof. Dr. med. BAR (cardiologist), REB (physician), and MLM (physician) - having extensive experience in the treatment of heart failure (HF) and cardiovascular imaging - agreed that the conceptual model is appropriate to reflect the progression from pre-HF to HF and the disease course of HF. Further, they agreed to the perspective, the time horizon, the costs, and the comparators for economic evaluation.

They suggested to include a health state of stage A HF (at risk of HF) to reflect a potential improvement of the GLS through intervention. Due to lack of appropriate data a health state of stage A HF was not included in the model, but the intervention effect was applied using HR on the HF incidence and mortality. In addition, testing the effect of a societal perspective was proposed. However, since HF usually affects patients at older age, no relevant impact of pre-HF screening on productivity losses was assumed. In addition, non-medical costs incurred by patients are assumed to be limited to co-payments. Thus, a societal perspective might likely not affect the overall results of this analysis.

A2/ Cross validation testing (conceptual model):

Has this model been compared to other conceptual models found in the literature or clinical textbooks?

The model structure has been compared to other conceptual models analyzing research questions in the field of HF treatment²⁷⁻²⁹. A concept representing disease progression by the number of HF hospitalizations with short- and long-term consequences of hospitalizations was chosen, as this reflects real disease progression most appropriately²⁸ and best modelled the course of the disease with the available data.

Part B: Input data validation

B1/ Face validity testing (input data):

Have experts been asked to judge the appropriateness of the input data?

Prof. Dr. med. SK (cardiologist), Prof. Dr. med. BAR (cardiologist), REB (physician), and MLM (physician) - having extensive experience in the treatment of HF and cardiovascular imaging - verified the appropriateness of the clinical input parameters, quality of life data, and data on resource utilization and costs as clinical experts. To avoid an underestimation of the risk of progression from pre-HF to HF obtained from a Danish population with a lower prevalence of risk factors than the HERZCHECK participants with pre-HF, monthly probabilities for pre-HF patients were based on the event rates of the worst GLS-quartile (GLS >-15.8%) in the Danish study. In addition, we tested the HF incidence in the deterministic sensitivity analysis and discussed its impact in the main text ('model validation', 'discussion').

B2/ Model fit testing:
When input parameters are based on regression models, have statistical tests been performed?
Short-term consequences of HF hospitalizations were modelled via log-normal and log-logistic curves. These were chosen based on results from di Tanna et al. who performed statistical tests and reported them as most appropriate (based on goodness-of-fit: AIC) ²⁸ . Utility values were mapped from results of the PROMIS-29 questionnaire using a mapping algorithm for German populations ¹⁶ that is recommended by HealthMeasures, the official information and distribution center for PROMIS ³⁰ .

Part C: Validation of the computerized model

C1/ External review:
Has the computerized model been examined by modelling experts?
The computerized model was built in TreeAge Pro Healthcare 2023 by one health economist who has completed the Online Advanced Healthcare Training by TreeAge (HK), and examined by a senior health economist (DM) with extensive experience in health economic modelling. In addition, a statistician (AS) checked the implementation of calculated input parameters/distributions/etc.. All were involved in the analysis.
C2/ Extreme value testing:
Has the model been run for specific, extreme sets of parameter values in order to detect any coding errors?
Extreme value testing was conducted by setting the treatment effect to zero. Results showed no difference in life years/QALYs/hospitalizations between the strategies. When additionally using zero costs of screening, intervention and pre-HF in the HERZCHECK strategy, no differences in costs and effects were observed. When only using zero costs of screening, intervention, and pre-HF in the HERZCHECK strategy with the effect left unchanged, a dominance of the HERZCHECK strategy was observed.
C3/ Testing of traces:
Have patients been tracked through the model to determine whether its logic is correct?
Patients were followed to assess the appropriateness of their disease progression. For example, the proportion of symptomatic HF patients after 11 years was investigated and compared to data of the Danish study used for GLS-based risks of pre-HF patients ⁴ . As expected, the proportion of symptomatic HF patients was slightly higher than that in the Danish study (10% vs. 6%), since HF incidence in the model was adjusted by age. In addition, it was tested and confirmed that patients who became symptomatic died at the same or a higher age than those who remained asymptomatic. Furthermore, the number of HF hospitalizations per patients were checked for plausibility.
C4/ Unit testing:
Have individual sub-modules of the computerized model been tested?
The discounting-module of the model was tested by running the model without global discounting. Average hospitalizations were in line with the number of hospitalizations saved in the corresponding tracker. In addition, each variable was checked for correct calculation and warnings.

Part D: Operational validation

D1/ Face validity testing (model outcomes):
Have experts been asked to judge the appropriateness of the model outcomes?
Prof. Dr. med. SK (cardiologist), Prof. Dr. med. BAR (cardiologist), REB (physician), and MLM (physician) - having extensive experience in the treatment of HF and cardiovascular imaging - agreed that the model results are reasonable for the broad screening population. Cost-effectiveness might be improved for more specific populations as seen in subgroup analyses.
D2/ Cross validation testing (model outcomes):
Have the model outcomes been compared to the outcomes of other models that address similar problems?
Model outcomes were compared to other models on screening for asymptomatic cardiac dysfunction. Results are presented in the main text ('discussion').
D3/ Validation against outcomes using alternative input data:
Have the model outcomes been compared to the outcomes obtained when using alternative input data?
Outcomes have been compared to those obtained when using alternative data for modelling the short-term implications of HF hospitalizations, applying the HF incidence and pre-HF mortality observed in the historical

control group of the HERZCHECK trial, and implementing an effect observed in the HERZCHECK trial. Overall results did not change: - Using data of a French study³¹ for log-logistic and log-normal modelling of the HF and mortality risk after a HF hospitalization resulted in a ICER comparable to the base case (66,450.99€/QALY). - Applying a higher HF incidence and pre-HF mortality observed in the historical control group of the HERZCHECK trial² resulted in a lower ICER than the base case (24,264.24€/QALY). This is reasonable, since a higher absolute number of HF cases could be delayed or prevented.
D4/ Validation against empirical data:
Have the model outcomes been compared to empirical data?
D4.A/ Comparison against the data sources on which the model is based (dependent validation).
- In the Danish study used for GLS-based risks of pre-HF patients, about 6.0% of the population developed symptomatic HF within median 11 years follow-up⁴. This proportion is lower than that observed in the model after 11 years (10%), resulting from the age adjustment applied in the model. - According to the proportion of inpatient and outpatient diagnoses applied on the HF incidence, ~40% of the patients in the model were diagnosed outpatient. - In line with the risk of HF hospitalization and death increasing with the number of HF hospitalizations, the age at death decreased with the number of HF hospitalization in the model.
D4.B/ Comparison against a data source that was not used to build the model (independent validation).
Some comparisons to empirical data are described in the main text ('model validation'). In addition, the following comparisons were conducted: - The age at which model patients died was slightly lower than the overall life expectancy (79.5 vs. 81.2 years³²) that might be due to the high cardiovascular risk of the HERZCHECK population. - The proportion of patients who died at an age of >100 years is higher than that reported for the German general population (1% vs. 0.03%)³³. This might result from the applied stable mortality at age ≥90 years in the model compared to an increase in general population. - In the model, symptomatic HF costs per year were approximately 2,600€. This is higher than the inflated HF costs reported by a German study in 2005 (2005: ~1,700€, 2023: 2,400€³⁴) that might result from developments in HF management and the inclusion of rehabilitation costs in the model.

Part E: Other validation techniques

E1/ Other validation techniques:
Have other validation techniques been performed?
We double checked the computerized model and input parameters and run all analyses several times.

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8. CHEERS

Topic	No.	Item	Location where item is reported
Title			
	1	Identify the study as an economic evaluation and specify the interventions being compared.	Title
Abstract			
	2	Provide a structured summary that highlights context, key methods, results, and alternative analyses.	Abstract
Introduction			
Background and objectives	3	Give the context for the study, the study question, and its practical relevance for decision making in policy or practice.	Introduction
Methods			
Health economic analysis plan	4	Indicate whether a health economic analysis plan was developed and where available.	Methods: p.5, l.10
Study population	5	Describe characteristics of the study population (such as age range, demographics, socioeconomic, or clinical characteristics).	Methods: p.5, ll.15ff.; supplementary material 1
Setting and location	6	Provide relevant contextual information that may influence findings.	Introduction; Methods: p. 5, ll.15ff.
Comparators	7	Describe the interventions or strategies being compared and why chosen.	Methods: p.6, ll.3ff., p.8, ll.10ff., p.9, ll.7ff.; supplementary material 4
Perspective	8	State the perspective(s) adopted by the study and why chosen.	Methods: p.5, ll.7ff.
Time horizon	9	State the time horizon for the study and why appropriate.	Methods: p.5, l.3
Discount rate	10	Report the discount rate(s) and reason chosen.	Methods: p.10, l.5
Selection of outcomes	11	Describe what outcomes were used as the measure(s) of benefit(s) and harm(s).	Methods: p.6, l.5, p.8, ll.10ff., p.10, ll.2ff.
Measurement of outcomes	12	Describe how outcomes used to capture benefit(s) and harm(s) were measured.	Methods: p.7, ll.12ff., p.8, ll.10ff.

Topic	No.	Item	Location where item is reported
Valuation of outcomes	13	Describe the population and methods used to measure and value outcomes.	Methods: p.8, ll.22ff.; supplementary material 3
Measurement and valuation of resources and costs	14	Describe how costs were valued.	Methods: p.9, ll.7ff.; supplementary material 4
Currency, price date, and conversion	15	Report the dates of the estimated resource quantities and unit costs, plus the currency and year of conversion.	Methods: p.9, ll.24f.
Rationale and description of model	16	If modelling is used, describe in detail and why used. Report if the model is publicly available and where it can be accessed.	Methods: p.6, ll.11ff.
Analytics and assumptions	17	Describe any methods for analysing or statistically transforming data, any extrapolation methods, and approaches for validating any model used.	Methods: p.6-9, p.10, ll.24ff.; supplementary material 2; supplementary material 7
Characterising heterogeneity	18	Describe any methods used for estimating how the results of the study vary for subgroups.	Methods: p.7, ll.12ff., p.10, ll.6f.
Characterising distributional effects	19	Describe how impacts are distributed across different individuals or adjustments made to reflect priority populations.	Methods: p.5, l.17, Discussion: p.18 ll.24ff.
Characterising uncertainty	20	Describe methods to characterise any sources of uncertainty in the analysis.	Methods: p.10, ll.10ff.
Approach to engagement with patients and others affected by the study	21	Describe any approaches to engage patients or service recipients, the general public, communities, or stakeholders (such as clinicians or payers) in the design of the study.	Supplementary material 7
Results			
Study parameters	22	Report all analytic inputs (such as values, ranges, references) including uncertainty or distributional assumptions.	Results: p.12, ll.2f., Table 1, Table 2
Summary of main results	23	Report the mean values for the main categories of costs and outcomes of interest and summarise them in the most appropriate overall measure.	Results: p.12, ll.8ff., Table 3
Effect of uncertainty	24	Describe how uncertainty about analytic judgments, inputs, or projections affect findings. Report the effect of choice of discount rate and time horizon, if applicable.	Results: p.12, ll.17ff., Table 3, Figure 2, Figure 3; supplementary material 5

Topic	No.	Item	Location where item is reported
Effect of engagement with patients and others affected by the study	25	Report on any difference patient/service recipient, general public, community, or stakeholder involvement made to the approach or findings of the study	Supplementary material 7
Discussion			
Study findings, limitations, generalisability, and current knowledge	26	Report key findings, limitations, ethical or equity considerations not captured, and how these could affect patients, policy, or practice.	Discussion
Other relevant information			
Source of funding	27	Describe how the study was funded and any role of the funder in the identification, design, conduct, and reporting of the analysis	Disclosures
Conflicts of interest	28	Report authors conflicts of interest according to journal or International Committee of Medical Journal Editors requirements.	Disclosures

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9. HEAP

Health Economic Analysis Plan (HEAP) for:

Health economic evaluation of the HERZCHECK program for detecting asymptomatic pre-heart failure compared to standard care in German high-risk patients – a microsimulation model

Project: "HERZCHECK" - Detection of Early Heart Failure Using Telemedicine in Structurally Weak Regions

NCT number: NCT05122793

Document date: 28.06.2024

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List of Abbreviations

ATC	Anatomical Therapeutic Chemical (Classification)
CEAC	Cost-Effectiveness Acceptability Curve
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CMR	Cardiac Magnetic Resonance Imaging
DRG	Diagnosis Related Group
EBM	Uniform Assessment Scale/Ambulatory Doctors Fee Schedule (Einheitlicher Bewertungsmaßstab)
EQ-5D	EuroQol-5D (preference-based measure of health related quality of life)
GBA	Federal Joint Commission (Gemeinsamer Bundesausschuss)
GLS	Global Longitudinal Strain
HEAP	Health Economic Analysis Plan
HF	Heart Failure
ICD	International Classification of Diseases
InEK	German Institute for the Hospital Renumeration System (Institut für das Entgelt-system im Krankenhaus)
IQWiG	Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen)
LVEF	Left Ventricular Ejection Fraction
PROMIS-29	Patient-Reported Outcomes Measurement Information Profile measure
PZN	Pharmacy Central Number
QALY	Quality Adjusted Life Year
RCT	Randomized Controlled Trial
SHI	Statutory Health Insurance
WTP	Willingness-To-Pay

Health economic evaluation of the HERZCHECK program for detecting asymptomatic pre-heart failure compared to standard care in German high risk patients – a microsimulation model: Health economic analysis plan (HEAP)

Section 1: Administrative Information

HEAP Version: 1.0, Date: 28 June 2024

This HEAP aims to describe the analysis and reporting procedure intended for the health economic modelling of the HERZCHECK trial (NCT05122793) to be undertaken. The analysis plan is designed to prevent bias in the results of the economic evaluation arising from selective reporting and to enable reproducibility.

This HEAP for the cost-effectiveness analysis incorporates elements from the method section in the Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS) statement¹ and from the HEAP template v1.0.² It was written before retrieving data from the HERZCHECK trial and the cooperating health insurance company (AOK Nordost). Thus, some aspects may be subject to change following initial exploratory analysis of trial and claims data.

This health economic evaluation is conducted as part of the HERZCHECK trial that is funded by the Innovation Committee of the Federal Joint Commission (Gemeinsamer Bundesausschuss (GBA); grant number: 01NVF19014).

Section 2: Introduction & background

Structural heart damage is possible even before the onset of typical heart failure (HF) symptoms. However, no screening measures for detection of early asymptomatic HF (pre-HF) are available yet.³ In this context, the Global Longitudinal Strain (GLS) gained importance. The GLS is an innovative and specific cardiac function parameter that enables to detect early structural heart damage before the onset of symptoms and has a higher predictive value than the common diagnostic parameter, the left ventricular ejection fraction (LVEF).⁴ Thus, the GLS is a valuable marker for detecting asymptomatic pre-HF.

The HERZCHECK trial aimed to investigate the effectiveness of a GLS-based screening via cardiac magnetic resonance imaging (CMR) for asymptomatic pre-HF in high-risk patients

(aged 40-69, at least one risk factor (diabetes mellitus/renal insufficiency/hypertension/obesity/hypercholesterolemia)). It includes i) an epidemiological study to determine the prevalence of asymptomatic pre-HF in structural weak regions in north-eastern Germany, and ii) a parallel design, two arm, randomized controlled trial (RCT) to determine whether an early diagnosis via GLS and subsequent prevention/therapy using telemedicine in structural weak regions improves the prognosis of HF patients compared to standard care.

Besides epidemiological and clinical data from the HERZCHECK trial, information on the long-term clinical and economic consequences is essential for the decision on the implementation of this screening-program in the German health care context.

Section 3: Aim of the economic evaluation & overview

Aim(s) of the economic evaluation

The aim of the economic evaluation is to investigate the lifetime cost-effectiveness and cost-utility of the HERZCHECK program (CMR + prevention/early therapy) compared with the current standard of care (no screening) in patients at risk for HF from the perspective of the German Statutory Health Insurance (SHI).

Objectives of the economic evaluation

The specific objectives of the health economic evaluation are

- i) to assess the long-term clinical consequences of GLS-based CMR-Screening for asymptomatic pre-HF and subsequent intervention versus standard care (=incremental effectiveness)
- ii) to assess the long-term costs of GLS-based CMR-Screening for asymptomatic pre-HF and subsequent intervention versus standard care (=incremental costs)
- iii) to estimate the incremental cost-effectiveness/cost-utility ratio of GLS-based CMR-Screening for asymptomatic pre-HF and subsequent intervention versus standard care in a high-risk population.

Type of economic analysis

The analytical approaches will take the form of cost-effectiveness and cost-utility analysis.

Population

The model population represents the HERZCHECK trial population: asymptomatic patients between the age of 40 to 69 years insured at the SHI with at least one of the following risk factors: diabetes mellitus, renal insufficiency, hypertension, obesity, hypercholesterolemia.

Intervention(s) and comparator(s)

Intervention: HERZCHECK program. Patients will receive a GLS-based screening via CMR and subsequently be categorized into no (A; $GLS < -15\%$), moderate (B; $-11\% \leq GLS < -15\%$) or severe (C; $GLS \geq -11\%$) asymptomatic pre-HF. Patients with moderate or severe asymptomatic pre-HF will be followed further in the health economic model. They will receive an innovative report of findings including the GLS, patient-friendly explanations of all CMR and laboratory results and recommendations for a healthy lifestyle including diet and exercise, as well as an early therapy initiation according to current clinical practice guidelines.

Comparator: Current standard of care without screening and no detection of early asymptomatic pre-HF.

Jurisdiction(s)

The evaluation setting is Germany, which has a SHI, providing solidarity-financed funded healthcare, primarily free of charge at the point of use.

Perspective(s)

The economic analysis will be conducted from the perspective of the SHI.

Time horizon(s)

The economic analysis will compare the costs and consequences of the HERZCHECK program versus standard care over a lifetime horizon.

Study design

Because the follow-up period of the HERZCHECK trial is only 1 year and effects of the screening are expected only in the mid- to long-term, a decision analytic model will be developed to evaluate long-term consequences of the HERZCHECK program.

Section 4: Modelling

Model type

A Markov model will be developed and a microsimulation with one month cycles will be performed to evaluate effects of the HERZCHECK program on costs and health benefits and its cost-effectiveness over the patient's lifetime.

Model structure

The decision model will compare the following strategies: i) no screening, ii) screening and prevention for moderate-severe asymptomatic pre-HF, and, if sufficient data is available, iii) screening and prevention for severe asymptomatic pre-HF. Each strategy will be structured as a model built around health states to which health care cost and health related outcome data will be linked.

To model the course of HF, a distinction is made between asymptomatic pre-HF patients, symptomatic patients in outpatient care and symptomatic patients in inpatient care. In each cycle, asymptomatic pre-HF patients can progress to a symptomatic health state, die or remain in the asymptomatic pre-HF state. Symptomatic patients can transfer between the symptomatic outpatient and inpatient health state or die. By definition, symptomatic HF patients cannot return to the asymptomatic pre-HF state.

Key assumptions

The main structural assumptions underpinning the decision model are listed below.

- Pathological GLS is associated with higher risk of symptom onset, hospitalizations and death.
- In standard care, HF is usually diagnosed only at symptom onset (i.e., pathological GLS remains unrecognized in standard care).
- The intervention group receives prevention measures/early therapy in the asymptomatic pre-HF state.
- The control group does not receive prevention measures/early therapy in the asymptomatic pre-HF state because pre-HF is unrecognized in standard care.
- Prevention measures/early therapy reduce the risk of symptom onset, hospitalizations (and death).
- The symptomatic HF state contains all patients which ever had symptoms (i.e., recently symptomatic in inpatient or outpatient care, or asymptomatic due to therapy).

- Prevention measures/early therapy are provided only in the asymptomatic pre-HF state.
- There is no risk reduction for the Intervention group in the symptomatic health states (i.e., same risks for control and intervention group).
- The diagnostic validity of GLS-determination within CMR in the study is comparable to that in the literature (100%).

Discount rates for costs and benefits

Costs and benefits will be discounted at the yearly rate recommended by current German guidelines (IQWiG) (as of June 2024: 3% per year, with Sensitivity Analyses testing 0 and 5%⁵).

Engagement with stakeholders

The model was conceptualized in consultation of clinical experts involved in the HERZCHECK trial. In addition, input parameters and results will be critically reviewed by clinical experts. Aspects corresponding to the implementation strategy of the HERZCHECK program (e.g., relevant resource use to be considered in intervention costs) will be discussed with clinical experts and the participating SHI company (AOK Nordost – Die Gesundheitskasse, Körperschaft des öffentlichen Rechts, Potsdam, Germany; payer).

Section 5: Data collection and management

Overview of data sources for identifying and estimating parameters

The lifetime cost-effectiveness of the HERZCHECK program will be evaluated using individual patient level data from the HERZCHECK trial, individual patient level claims data and literature.

The model will require several main sets of parameters: 1) Transition probabilities, 2) Treatment effect, 3) Quality of Life, 4) Costs.

Transition probabilities between the health states will be obtained from literature and HERZCHECK trial data. They will be estimated by sex and age groups where possible. Further, for asymptomatic pre-HF patients transition probabilities will be based on the GLS and sex, and for symptomatic patients on the number of hospitalizations and the time since the last hospitalization where possible. Mortality rates will be based on age where possible. The treatment effect of the intervention will be obtained from HERZCHECK trial data. Quality of Life (i.e., utilities) data will be obtained from HERZCHECK trial data and/or literature (including mapping where

necessary). Costs of asymptomatic pre-HF patients will be obtained from claims data. Costs of symptomatic patients will be obtained from claims data, public data and literature. Intervention costs will be derived from HERZCHECK trial data and public data.

Appropriate literature will be identified via systematic literature searches. Selection criteria will be the methodological quality and representativeness for the context of the analysis. Systematic reviews will be preferred according to methodological guidelines⁶, but other study designs are not excluded.

If a model parameter cannot be obtained from HERZCHECK trial data, claims data or the literature, it will be parameterized using expert opinion where necessary.

Identification of resources

The following items of health care resources are suspected to differ between the intervention and control group and are therefore considered in the model: outpatient office visits, medication, hospitalizations, rehabilitation. The use of these health care resources will be obtained from claims data and literature.

Furthermore, resource use required for the delivery of the intervention will be considered to assess the intervention costs. Relevant resource use associated with the intervention will be derived from HERZCHECK trial data and determined regarding a realistic implementation in standard care in consultation of clinical experts and experts from the SHI. For example, only laboratory parameters that should be explicitly examined in combination with the CMR and are not tested in standard care yet will be considered in intervention costs.

Measurement of resource-use data

For the intervention group, resource-use of asymptomatic pre-HF patients will be collected using claims data that will be provided for all HERZCHECK trial participants included in the RCT. The patient-specific claims data period is 24 months before to 12 months after the first HERZCHECK CMR exam. To be able to allocate resource use to health states, the claims data will be linked to HERZCHECK trial data based on the study pseudonyms as well as sex and year of birth. HERZCHECK trial data will be provided for all study participants that are included in the RCT and are insured at participating SHI company (AOK Nordost). They will include for example the study pseudonym, the year of birth, sex, date of CMR, the GLS, study group and quality of life data.

Long-term healthcare resource-use of symptomatic patients will be collected from further claims data of heart failure patients and added by literature and public data where necessary. Claims data of heart failure patients will be provided by the participating SHI company (AOK Nordost) for a group of incident HF patients that were diagnosed between 2014 and 2022 and were comparable to the HERZCHECK trial population at risk in 2013 (e.g., regarding comorbidities, age group, sex).

The extent of relevant resource use required for the delivery of the intervention will be determined in consultation of clinical experts and experts from the SHI.

For the control group, no HF specific resource-use is assumed in asymptomatic pre-HF patients. Symptomatic patients in the control group are assumed to have the same resource-use as symptomatic patients in the intervention group.

Valuation of resource-use data

For the intervention group, healthcare costs of asymptomatic pre-HF patients will be obtained from claims data of the participating SHI company (AOK Nordost).

Costs of symptomatic patients will be obtained from claims data of the participating SHI company (AOK Nordost), literature and public data. In particular, hospitalization costs will be obtained from claims data or InEK (German Institute for the Hospital Remuneration System) data (i.e., DRG reference costs). Rehabilitation costs will be calculated using literature-based German daily rates. Costs for outpatient visits will be calculated via literature-based German assessment rates or be obtained from claims data. Medication costs will be obtained from claims data or calculated using German drug prices.

A random validation of the costs submitted in the claims data will be conducted. For example, outpatient resource use will be valued in monetary terms using the EBM (uniform assessment scale)/Germany daily rates and DRG reference costs (InEK data) will be used to value hospital resource-use (e.g., inpatient stays).

Resource use associated with the intervention will be valued using different data sources, such as internal HERZCHECK trial data, comparable public available selective contracts for CMR examinations and German prices for health services (EBM).

For the control group, no HF specific costs are assumed in asymptomatic pre-HF patients. Symptomatic patients in the control group are assumed to have the same costs as symptomatic patients in the intervention group.

All resource use will be valued in monetary terms using appropriate German unit costs (€) at the time of analysis (2023/2024). Adjustments will be made for inflation as recommended by the IQWiG (as of June 2024: using the consumer price index of the Federal Statistical Office⁵).

Identification of outcome(s)

The primary outcome measure in the economic evaluation will be Life Years gained. Secondary outcomes will measure prevented HF hospitalizations and gained quality adjusted life years (QALYs) (i.e., combined outcome of quality of life and life expectancy). These outcomes were chosen because the HERZCHECK program aims to improve the patients' prognosis and life expectancy and reduce hospitalizations.

Measurement of outcome(s)

Life years gained and prevented HF hospitalizations will be measured by modelling the disease progression in terms of symptom onset and number of hospitalizations, and patients' mortality. Lifetime disease progression and mortality will be modelled using HERZCHECK trial data (follow-up of 12 months) and literature. Thereby, probabilities of symptom onset will be based on the GLS and sex and probabilities of disease progression will be based on the number of hospitalizations and the time since the last hospitalization where possible. Mortality rates will be age-dependent where possible. Life years and number of hospitalizations in the intervention and control group will be summed up over the modelling period and compared with each other to examine the difference between the strategies.

Valuation of outcome(s)

QALYs will be calculated by multiplying utility scores of specific health states with the time spent in the respective state.

Utility scores will be derived from HERZCHECK trial data (PROMIS-29) and literature. If quality of life data is not available as utilities, a mapping will be performed using appropriate algorithms. For example, PROMIS-29 responses from HERZCHECK participants may be mapped to EQ-5D via the published mapping algorithm for Germany by Klapproth et al. (2020)⁷ to obtain utilities.

Transition probabilities

Transition probabilities will be determined using appropriate statistical methods based on HERZCHECK trial data, claims data and appropriate literature.

A few examples: Probabilities and rates will be transformed to probabilities corresponding to the cycle length using generally accepted methods⁸. If necessary, all-cause mortality obtained from national life tables will be added to disease-specific mortality. Thereby, all-cause mortality will be corrected for disease-specific mortality, as cardiovascular disease/HF represent a major cause of death in the target population.

Treatment effect

The hazard ratio for disease specific morbidity observed during the trial will be assumed to persist after the end of trial follow up. However, the duration and a possible reduction of the treatment effect have yet to be defined and will depend on the results of the RCT.

Section 6: Statistical analysis

Statistical software

IBM SPSS Statistics for Windows (Version 29.0.0.0 or higher) and R (version 4.2.2 or higher) will be used for data preparation and parametrization. TreeAge Pro (2023 or higher) will be used for the decision analytic modelling.

Analysis of resource use, costs and outcomes

Mean differences in costs, QALYs, life years and hospitalizations between the treatment groups will be estimated and presented. No statistical comparison will be conducted.

Analysis of cost-effectiveness

Cost and outcome data (QALYs, Life Years, Hospitalizations) will be combined to calculate an incremental cost-effectiveness ratio (ICER) statistic from the SHI perspective.

Because there is no commonly accepted willingness-to-pay (WTP) threshold for Germany, the estimated mean costs, QALYs, life years and hospitalizations associated with each treatment option will be combined with a feasible range of values for decision makers' WTP, to obtain the probability of cost-effectiveness at different levels of WTP.

Data cleaning

All data will be checked for completeness and face validity and plausibility tests will be performed (e.g., to identify misspelt text, missing values or outlier). Any anomalies will be discussed with the unit supplying the data. Corrections made will be documented.

Missing data

HERZCHECK trial data and claims data will be examined for any missing data. The appropriate method for dealing with missing data will depend on the proportion, the type and the likely mechanism of missing data. In the case of randomly missing data, an imputation (e.g., adding the Anatomical Therapeutic Chemical (ATC) Classification via the pharmacy central number (PZN) using the Lauer-Taxe) or exclusion for the analysis will be carried out, depending on the possibilities. Corrections made will be documented.

Uncertainty

Deterministic and probabilistic sensitivity analyses will be performed to explore the robustness of the evaluation results. This will involve making plausible changes to input parameters and methodological assumptions to investigate the impact of these changes on the model results. Examples: variation of intervention costs; different approaches of modelling the treatment effect; variation of discount rates.

Results of the probabilistic sensitivity analysis will be presented as scatterplot and/or as cost-effectiveness-acceptability curve (CEAC) that shows the probability of cost-effectiveness for different WTP thresholds.

Heterogeneity

Heterogeneity of the model population will be incorporated via a microsimulation that considers time-dependent risks and risks dependent on the GLS, age, sex and number of previous hospitalizations.

On the final dataset, subgroup analyses will investigate how cost-effectiveness varies depending on patient characteristics, such as age, sex, GLS. Any subgroup analyses for which the smaller subgroup includes fewer than 5 participants will be omitted.

Model validation

The model will be estimated and internally validated using HERZCHECK trial data, expert opinion and literature. Validation will be performed and reported following the AdViSHE Validation-Assessment Tool of Health-Economic Models for Decision Makers and Model Users⁹.

Section 7: Reporting

CHEERS 2022 guidelines will be followed when reporting the health economic evaluation.

Section 8: Roles and responsibilities

This HEAP was prepared by HK (junior health economist) and approved by Dr DM (senior health economist). The trial health economist(s) are responsible for conducting and reporting the economic evaluation in accordance with the HEAP.

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Dr. rer. pol. Dirk Müller

Senior health economist

Cologne, 28th June 2024

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Supplementary material to chapter 5.3 (DP III)

The supplementary material presented in this appendix has been previously published in ‘Clinical Research in Cardiology’ (2025, 114:1718-1729, doi:10.1007/s00392-025-02655-y).

Sex differences in guideline adherence for coronary angiography in patients with suspected chronic coronary syndrome in Germany: insights from the ENLIGHT-KHK trial - Supplementary Material

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Supplementary Text S1: Details on regression analysis

For all regression models, covariates with > 2 categories were transformed into dummy variables. In addition, it was checked for the basic assumptions for conducting logistic regression (i.e., independence of errors, linearity in the logit for any continuous independent variable, lack of strongly influential outliers and absence of multicollinearity or redundancy¹). All basic assumptions for logistic regression were fulfilled. Stepwise backward regression was conducted by starting with a full model that included all variables and gradually eliminating the least promising ones using the prespecified significance level¹ 0.05.

Supplementary Table S1: Baseline characteristics and coronary angiography results before Benjamini-Hochberg adjustment

Baseline characteristics of participants	Total (n=659)	Women (n=273)	Men (n=386)	P-value
Age (years), mean (SD)	66.5 (10.4)	68.9 (10.0)	64.8 (10.4)	<0.001*
BMI, mean (SD)	29.6 (5.9)	29.9 (6.4)	29.4 (5.5)	0.649
Number of risk factors; n (%)				0.357
0	6 (0.9)	2 (0.7)	4 (1.4)	
1-2	158 (24.0)	73 (26.7)	85 (22.0)	
≥3	495 (75.1)	198 (72.5)	297 (76.9)	
Cardiovascular risk factors; n (%)				
Diabetes mellitus	218 (33.1)	79 (28.9)	139 (36.0)	0.057
Smoking ^a	344 (52.2)	104 (38.1)	240 (62.2)	<0.001*
Overweight	519 (78.8)	212 (77.7)	307 (79.5)	0.562
Family history	210 (31.9)	98 (35.9)	112 (29.0)	0.062
Hypertension	549 (83.3)	236 (86.5)	313 (81.1)	0.069
Hypercholesterolaemia	366 (55.5)	150 (55.0)	216 (56.0)	0.796
Comorbidities; n (%)				
CAD history	335 (50.8)	114 (41.8)	221 (57.3)	<0.001*
Chronic renal failure	47 (7.1)	16 (5.9)	31 (8.0)	0.286
Respiratory disease	109 (16.5)	47 (17.2)	62 (16.1)	0.695
Peripheral artery disease	61 (9.3)	20 (7.3)	41 (10.6)	0.150
Depression	30 (4.6)	15 (5.5)	15 (3.9)	0.329
Complaints type; n (%)				0.930
Typical angina	224 (34.0)	95 (34.8)	129 (33.4)	
Atypical angina	270 (41.0)	110 (40.3)	160 (41.5)	
Non-anginal thoracic constraints	165 (25.0)	68 (24.9)	97 (25.1)	
Symptom severity; n (%)				0.093
CCS-Grade 0	52 (7.9)	17 (6.2)	35 (9.1)	
CCS-Grade 1	110 (16.7)	36 (13.2)	74 (19.2)	
CCS-Grade 2	205 (31.1)	94 (34.4)	111 (28.8)	
CCS-Grade 3	230 (32.9)	99 (36.3)	131 (33.9)	
CCS-Grade 4 ^b	62 (9.4)	27 (9.9)	35 (9.1)	
Non-invasive test; n (%)	237 (36.0)	86 (31.5)	151 (39.1)	0.045*
Non-invasive test result ^c ; n (%)				0.493
Positive	130 (19.7)	43 (15.8)	87 (22.5)	
Negative	37 (5.6)	15 (5.5)	22 (5.7)	
unclear	69 (10.5)	28 (10.3)	41 (10.6)	
Pre-test probability; n (%)				<0.001*
Low (<15%)	14 (2.1)	14 (5.1)	0 (0.0)	
Intermediate (15-85%)	600 (91.0)	259 (94.9)	341 (88.3)	
High (≥85%)	45 (6.8)	0 (0.0)	45 (11.7)	
Coronary angiography				
Guideline adherent	169 (25.6)	53 (19.4)	116 (30.1)	0.002
CAD	424 (64.3)	138 (50.5)	286 (74.1)	<0.001

^a ever (current or in the past), ^b Patients reporting symptoms at rest but without acute coronary syndrome, ^c result of one man missing

BMI = Body Mass Index, CAD = Coronary Artery Disease, CCS = Canadian Cardiovascular Society, SD = Standard Deviation

Supplementary Tables S2: Regression results before Benjamini-Hochberg adjustment

S2.1. Multiple binary logistic regression analysis for guideline adherence

Variable ^{c,d}	Model 1 ^a				Model 2 ^b			
	OR	95% CI	P-value	Nagelkerke R ²	OR	95% CI	P-value	Nagelkerke R ²
Sex	0.40	0.23 -0.69	0.001	0.628	0.44	0.30-0.66	<0.001	0.114
Age (in years)	1.09	1.06-1.12	<0.001		1.04	1.02-1.06	<0.001	
Diabetes mellitus	1.76	1.00-3.10	0.049					
Smoking								
Overweight								
Family history								
Hypertension					0.46	0.29-0.74	0.001	
Hypercholesterolaemia								
CAD history					0.58	0.39-0.85	0.005	
Chronic renal failure								
Respiratory disease								
Peripheral artery disease								
Depression								
Typical angina	4.72	2.63-8.47	<0.001		1.96	1.35-2.86	<0.001	
Atypical angina								
CCS-Grade 0								
CCS-Grade 1								
CCS-Grade 3					0.64	0.43-0.97	0.033	
CCS-Grade 4 ^e								
Non-invasive testing	33.06	15.33-71.29	<0.001					
Non-invasive test result positive	5.72	2.77-11.78	<0.001					
Non-invasive test result negative	0.13	0.04-0.40	<0.001					

^a Final model: chi-square 366.980, p<0.001

^b Final model: chi-square 53.215, p<0.001

^c Redundant variables were excluded: non-anginal thoracic constraints, CCS-Grade 2, non-invasive test result unclear

^d for sex: male sex as reference category; for all other variables: factor/disease not prevalent as reference category

^e Patients reporting symptoms at rest but without acute coronary syndrome

CAD = Coronary Artery Disease, CCS = Canadian Cardiovascular Society, CI = Confidence Interval, OR = Odds Ratio

S2.2. Multiple binary logistic regression analysis for guideline adherence, separated for women and men

	Women				Men			
	OR	95% CI	P-value	Nagelkerke R ²	OR	95% CI	P-value	Nagelkerke R ²
Variable^{a,b}	Model 1-f^c			0.634	Model 1-m^d			0.613
Age (in years)					1.11	1.07-1.15	<0.001	
Diabetes mellitus	3.68	1.33-10.21	0.012					
Respiratory disease	3.13	1.06-9.23	0.038					
Smoking					0.48	0.25-0.92	0.027	
Typical angina					8.46	4.02-17.79	<0.001	
Non-invasive testing					14.19	5.49-36.71	<0.001	
Non-invasive test result positive	173.27	50.02-600.18	<0.001		7.94	2.97-21.22	<0.001	
Non-invasive test result negative					0.22	0.05-0.97	0.045	
CCS-Grade 4 ^e	4.40	1.23-15.71	0.023					
CAD history	0.23	0.08-0.68	0.008					
Variable^{a,b}	Model 2-f^c			0.066	Model 2-m^g			0.260
Overweight	0.42	0.22-0.81	0.010					
Age (in years)					1.07	1.04-1.10	<0.001	
Smoking					0.55	0.34-0.91	0.019	
Typical Angina					3.58	2.15-5.97	<0.001	
Hypertension					0.30	0.17-0.56	<0.001	
CAD history	0.48	0.25-0.93	0.028		0.52	0.31-0.86	0.011	
CCS-Grade 3					0.51	0.30-0.89	0.017	

^a Redundant variables were excluded: CCS-Grade 2, non-invasive test result unclear, non-anginal thoracic constraints (men)/atypical angina (women)

^b for all variables: factor/disease not prevalent as reference category

^c Final model: chi-square 138.094, p<0.001

^d Final model: chi-square 218.580, p<0.001

^e Patients reporting symptoms at rest but without acute coronary syndrome

^f Final model: chi-square 11.467, p=0.003

^g Final model: chi-square 78.062, p<0.001

CAD = Coronary Artery Disease, CCS = Canadian Cardiovascular Society, CI = Confidence Interval, OR = Odds Ratio

Supplementary Tables S3: Results of the first step of regression

S3.1. Multiple binary logistic backwards regression analysis for guideline adherence

Variable ^{a,b}	Model 1				Model 2			
	OR	95% CI	P-value	Nagelkerke R ²	OR	95% CI	P-value	Nagelkerke R ²
Sex	0.35	0.19-0.64	<0.001	0.651	0.40	0.26-0.61	<0.001	0.136
Age (in years)	1.08	1.05-1.12	<0.001		1.03	1.01-1.05	0.008	
Diabetes mellitus	1.85	1.01-3.38	0.046		1.24	0.83-1.87	0.297	
Smoking	0.59	0.33-1.08	0.085		0.65	0.43-0.99	0.043	
Overweight	0.81	0.43-1.54	0.515		0.78	0.50-1.23	0.291	
Family history of CAD	0.88	0.48-1.61	0.679		1.14	0.75-1.74	0.537	
Hypertension	0.83	0.40-1.73	0.620		0.48	0.29-0.78	0.003	
Hypercholesterolaemia	0.79	0.45-1.39	0.414		1.15	0.78-1.70	0.480	
CAD history	0.99	0.55-1.79	0.963		0.57	0.38-0.85	0.006	
Chronic renal failure	0.79	0.26-2.45	0.686		1.09	0.53-2.27	0.814	
Respiratory disease	1.26	0.59-2.69	0.547		1.39	0.83-2.31	0.207	
Peripheral artery disease	2.08	0.84-5.15	0.114		1.05	0.55-2.02	0.883	
Depression	2.84	0.74-10.85	0.128		1.17	0.47-2.95	0.733	
Typical angina	3.33	1.53-7.25	0.002		1.80	1.08-2.99	0.024	
Atypical angina	0.51	0.24-1.08	0.079		0.83	0.50-1.37	0.468	
CCS-Grade 0	1.58	0.53-4.73	0.417		1.34	0.65-2.76	0.435	
CCS-Grade 1	0.56	0.23-1.36	0.199		0.73	0.40-1.32	0.293	
CCS-Grade 3	0.92	0.47-1.81	0.803		0.63	0.39-1.00	0.052	
CCS-Grade 4 ^c	1.93	0.78-4.82	0.157		1.17	0.62-2.24	0.628	
Non-invasive testing	37.61	16.53-85.55	<0.001		-	-	-	
Non-invasive test result positive	6.43	2.97-13.92	<0.001		-	-	-	
Non-invasive test result negative	0.15	0.05-0.46	0.001		-	-	-	

^a Redundant variables were excluded: non-anginal thoracic constraints, CCS-Grade 2, non-invasive test result unclear

^b for sex: male sex as reference category; for all other variables: factor/disease not prevalent as reference category

^c Patients reporting symptoms at rest but without acute coronary syndrome

CAD = Coronary Artery Disease, CCS = Canadian Cardiovascular Society, CI = Confidence Interval, OR = Odds Ratio

S3.2. Multiple binary logistic backwards regression analysis for guideline adherence in women

Variable ^{a,b}	Model 1-f				Model 2-f			
	OR	95% CI	P-value	Nagelkerke R ²	OR	95% CI	P-value	Nagelkerke R ²
Age (in years)	1.09	0.95-1.26	0.226	0.890	0.96	0.93-1.00	0.049	0.182
Diabetes mellitus	51.15	2.41-1087.54	0.012		2.32	1.11-4.84	0.026	
Smoking	1.31	0.2-8.76	0.781		0.92	0.43-1.98	0.826	
Overweight	0.16	0.02-1.27	0.082		0.29	0.14-0.62	0.001	
Family history of CAD	0.72	0.10-5.09	0.743		0.83	0.40-1.72	0.618	
Hypertension	0.74	0.09-6.32	0.785		0.83	0.33-2.08	0.689	
Hypercholesterolaemia	0.71	0.13-3.83	0.693		0.98	0.50-1.94	0.959	
CAD history	0.52	0.08-3.55	0.501		0.49	0.23-1.04	0.064	
Chronic renal failure	2.69	0.00-6.03E+40	0.983		0.47	0.09-2.52	0.379	
Respiratory disease	1.18	0.13-10.74	0.884		1.90	0.79-4.58	0.155	
Peripheral artery disease	2.32	0.07-75.95	0.637		0.26	0.05-1.36	0.111	
Depression	23882145.48	-	0.993		1.78	0.48-6.56	0.385	
Typical angina	0.89	0.09-8.77	0.920		0.62	0.28-1.39	0.245	
Non-anginal thoracic constraints	20.54	0.66-642.83	0.085		1.01	0.45-2.28	0.984	
CCS-Grade 0	100.06	0.20-51085.52	0.148		3.07	0.85-11.05	0.086	
CCS-Grade 1	0.62	0.05-8.08	0.715		0.70	0.22-2.26	0.555	
CCS-Grade 3	3.55	0.38-33.13	0.266		1.13	0.50-2.58	0.769	
CCS-Grade 4 ^c	87.34	1.46-5234.99	0.032		2.63	0.89-7.80	0.081	
Non-invasive testing	2.67E+16	-	0.989		-	-	-	
Non-invasive test result positive	17.58	2.38-129.88	0.005		-	-	-	
Non-invasive test result negative	0.00	0.00-0.18	0.007		-	-	-	

^a Redundant variables were excluded: CCS-Grade 2, non-invasive test result unclear, non-anginal thoracic constraints (men)/atypical angina (women)

^b for all variables: factor/disease not prevalent as reference category

^c Patients reporting symptoms at rest but without acute coronary syndrome

CAD = Coronary Artery Disease, CCS = Canadian Cardiovascular Society, CI = Confidence Interval, OR = Odds Ratio

S3.3. Multiple binary logistic backwards regression analysis for guideline adherence in men

Variable^{a,b}	Model 1-m				Model 2-m			
	OR	95% CI	P-value	Nagelkerke R ²	OR	95% CI	P-value	Nagelkerke R ²
Age (in years)	1.11	1.07-1.16	<0.001	0.639	1.08	1.05-1.11	<0.001	0.284
Diabetes mellitus	1.50	0.71-3.14	0.288		1.09	0.63-1.89	0.770	
Smoking	0.40	0.20-0.81	0.011		0.49	0.29-0.82	0.007	
Overweight	1.10	0.47-2.58	0.823		1.41	0.74-2.68	0.295	
Family history of CAD	1.58	0.73-3.45	0.247		1.70	0.94-3.05	0.077	
Hypertension	0.53	0.22-1.29	0.159		0.27	0.14-0.52	<0.001	
Hypercholesterolaemia	1.08	0.53-2.20	0.835		1.34	0.78-2.28	0.287	
CAD history	0.88	0.41-1.87	0.734		0.46	0.27-0.80	0.006	
Chronic renal failure	1.23	0.35-4.26	0.746		1.45	0.57-3.68	0.440	
Respiratory disease	0.97	0.38-2.46	0.946		1.26	0.63-2.49	0.515	
Peripheral artery disease	2.11	0.75-5.89	0.156		1.21	0.52-2.83	0.655	
Depression	1.54	0.19-12.77	0.691		1.15	0.26-5.08	0.858	
Typical angina	6.69	2.46-18.22	<0.001		3.26	1.58-6.74	0.001	
Atypical angina	0.55	0.22-1.41	0.215		0.77	0.38-1.54	0.458	
CCS-Grade 0	1.07	0.27-4.31	0.926		1.02	0.38-2.75	0.976	
CCS-Grade 1	0.48	0.16-1.43	0.188		0.81	0.37-1.76	0.590	
CCS-Grade 3	0.55	0.23-1.27	0.161		0.46	0.24-0.88	0.019	
CCS-Grade 4 ^c	1.33	0.41-4.26	0.635		0.90	0.36-2.24	0.826	
Non-invasive testing	16.60	5.89-46.78	<0.001		-	-	-	
Non-invasive test result positive	6.65	2.32-19.04	<0.001		-	-	-	
Non-invasive test result negative	0.29	0.06-1.36	0.117		-	-	-	

^a Redundant variables were excluded: CCS-Grade 2, non-invasive test result unclear, non-anginal thoracic constraints (men)/atypical angina (women)

^b for all variables: factor/disease not prevalent as reference category

^c Patients reporting symptoms at rest but without acute coronary syndrome

CAD = Coronary Artery Disease, CCS = Canadian Cardiovascular Society, CI = Confidence Interval, OR = Odds Ratio

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Doctoral student's declaration of contribution

Doctoral student's declaration of contribution

1. HERZCHECK: Early Detection of Subclinical Heart Failure Using Mobile Cardiac Magnetic Resonance and Telemedicine in Rural and Underresourced Regions

Sebastian Kelle and Maximilian Leo Müller and Rebecca Elisabeth Beyer, Gisela Thiede, Anna Clara Nolden, Henning Steen, Bjoern Andrew Remppis, Johannes Wieditz, Alex Tuit, Mina Cvetkovic, Patrick Doeblin, Undine Ella Witt, Florian André, Sein Schmidt, Alexander Huppertz, Dusan Simic, Dirk Müller, Arim Shukri, Katrin Christian Reber, Ulf Landmesser, Norbert Frey, Burkert Pieske, Eike Nagel, Stephanie Stock, Volkmar Falk, Hannah Kentenich and Tim Friede on behalf of the HERZCHECK consortium

Circulation: Heart Failure [Impact Factor at time of publication: 8.3]

Author's contributions

Sebastian Kelle, Gisela Thiede, Henning Steen, Bjoern Andrew Remppis, Alexander Huppertz, Dusan Simic, Katrin Christiane Reber, Ulf Landmesser, Norbert Frey, Burkert Pieske, Eike Nagel, Stephanie Stock, Volkmar Falk, and Tim Friede conceived and designed the study. Sebastian Kelle, Maximilian Leo Müller, Rebecca Elisabeth Beyer, Gisela Thiede, Anna Clara Nolden, Alex Tuit, Mina Cvetkovic, Undine Ella Witt, and Katrin Christiane Reber collected the data. Sebastian Kelle, Maximilian Leo Müller, Rebecca Elisabeth Beyer, Anna Clara Nolden, Johannes Wieditz, Alex Tuit, Mina Cvetkovic, Undine Ella Witt, Alexander Huppertz, Dusan Simic, Dirk Müller, Arim Shukri, Stephanie Stock, Hannah Kentenich, and Tim Friede performed the analyses. Hannah Kentenich, Dusan Simic and Arim Shukri designed and conceptualized the analysis on time gained for prevention. Hannah Kentenich has performed all analyses on the time gained for prevention and adverse events (including technical validation of data) with statistical support by Arim Shukri. Sebastian Kelle, Maximilian Leo Müller, Rebecca Elisabeth Beyer, Johannes Wieditz, Hannah Kentenich, and Tim Friede wrote the first draft of the manuscript. All authors critically reviewed the manuscript and provided intellectual input. All authors gave final approval for the publication of the manuscript.

2. Cost-Effectiveness of a Global Longitudinal Strain-Based Screening and Prevention Program for Pre-Heart Failure Compared With Standard of Care

Hannah Kentenich, Sebastian Kelle, Rebecca Elisabeth Beyer, Maximilian Leo Müller, Bjoern Andrew Remppis, Tim Friede, Dusan Simic, Stephanie Stock, Arim Shukri, Dirk Müller and the HERZCHECK group*

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Value in Health [Impact Factor at time of publication: 6.0]

Author's contributions

Hannah Kentenich and Dirk Müller designed the decision-analytic model and acquired, analyzed, and interpreted the data. Hannah Kentenich conducted the model parametrization with statistical support by Arim Shukri. Sebastian Kelle, Maximilian Leo Müller, Rebecca Elisabeth Beyer, and Bjoern Andrew Remppis verified and validated the model structure, input data, and results. Hannah Kentenich wrote the first draft of the manuscript. Dirk Müller and Arim Shukri revised the manuscript. Dirk Müller and Stephanie Stock supervised the economic analysis. Sebastian Kelle, Gisela Thiede, Henning Steen, Bjoern Andrew Remppis, Dusan Simic, Stephanie Stock, and Tim Friede conceived and designed the HERZCHECK trial. Sebastian Kelle, Maximilian Leo Müller, Rebecca Elisabeth Beyer, Anna Clara Nolden, Gisela Thiede, Diana Graja, and Stephanie Sehlen collected data in the HERZCHECK trial. Johannes Wieditz evaluated and provided the HERZCHECK trial data. All authors read and approved the final manuscript.

3. Sex differences in guideline adherence for coronary angiography in patients with suspected chronic coronary syndrome in Germany: insights from the ENLIGHT-KHK trial

Hannah Kentenich, Arim Shukri, Dirk Müller, Bastian Wein, Oliver Bruder, Stephanie Stock, Yana Kampfer

Clinical Research in Cardiology [Impact Factor at time of publication: 3.8]

Author's contributions

Hannah Kentenich, Yana Kampfer and Arim Shukri were involved in the conceptualization and methodology of this analysis. The data analysis was conducted by Hannah Kentenich and was supported statistically by Arim Shukri and in terms of content by Yana Kampfer. Bastian Wein supported with his clinical expertise and validation. All authors contributed to the data interpretation. Hannah Kentenich wrote the first draft of the manuscript. Hannah Kentenich and Yana Kampfer wrote the final manuscript. Dirk Müller, Arim Shukri and Bastian Wein reviewed and revised the manuscript. Oliver Bruder and Stephanie Stock supervised the analysis. All authors read and approved the final manuscript.



Curriculum Vitae

Curriculum Vitae

Mein Lebenslauf wird aus Gründen des Datenschutzes in der elektronischen Fassung meiner Arbeit nicht veröffentlicht.

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Eidesstattliche Erklärung

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Übersicht der Publikationen:

- 1) Kelle S, Müller ML, Beyer RE, et al. HERZCHECK: Early Detection of Subclinical Heart Failure Using Mobile Cardiac Magnetic Resonance and Telemedicine in Rural and Underresourced Regions. *Circ Heart Fail*. 2026;19(8):e013935. doi:10.1161/CIR-CHEARTFAILURE.125.013935
- 2) Kentenich H, Kelle S, Beyer RE, et al. Cost-Effectiveness of a Global Longitudinal Strain-Based Screening and Prevention Program for Pre-Heart Failure Compared With Standard of Care. *Value Health*. 2026;29(9):1560-1570. doi:10.1016/j.jval.2026.04.002
- 3) Kentenich H, Shukri A, Müller D, et al. Sex differences in guideline adherence for coronary angiography in patients with suspected chronic coronary syndrome in Germany: insights from the ENLIGHT-KHK trial. *Clin Res Cardiol*. 2025;114:1718-1729. doi:10.1007/s00392-025-02655-y

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