

## CLCZ696BDE06 Study Results Abstract for Public Disclosure

### Title

Characterizing guideline-adherent option and treatment quality in clinical routine of German HFrEF care in heart failure units and independent centers utilizing established quality indicators

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### NIS Type

NIS with primary data collection

### Keywords

Chronic heart failure, heart failure with reduced ejection fraction, primary care in Germany, guideline-directed medical therapy

### Rationale and background

Heart failure (HF) is a debilitating and life-threatening condition, which impacts over 64 million people worldwide and results in recurrent hospitalizations and increased risk for mortality (James et al., 2018). The most serious subtype is heart failure with reduced ejection fraction (HFrEF) with  $\leq 40\%$  left ventricular ejection fraction remaining.

For these patients the current guideline of the European Society of Cardiology (ESC) recommends a quadruple therapy comprising angiotensin-converting enzyme inhibitors (ACE-I) or an angiotensin receptor-neprilysin inhibitor (ARNI), beta-blockers (BB), mineralocorticoid receptor antagonists (MRA) with the addition of sodium-glucose co-transporter 2 inhibitors (SGLT2i) dapagliflozin and empagliflozin (McDonagh et al., 2021). Further, in patients with signs of congestion, diuretics should be added. Depending on treatment response and clinical phenotype, cardiac implanted devices should be considered, e.g. implantable cardioverter defibrillator (ICD), cardiac resynchronization therapy (CRT), or their combination Cardiac Resynchronization Therapy with Defibrillator (CRT-D).

Despite the availability of the above-mentioned disease modifying treatment options, outcomes still remain suboptimal, with high rates of rehospitalization and death (Shah et al., 2017). This is due, in part, to inadequate adoption of guideline-directed medical therapy (GDMT) and lacking structures supporting regular post-discharge patient follow-up and/or remote patient monitoring (Greene et al., 2018).

Besides these well-established and evidence-based treatment options, the benefits and importance of multidisciplinary HF management are emphasized by guidelines to reduce long term outcomes such as hospitalizations and mortality in patients with HF (McDonagh et al., 2021). Multidisciplinary HF management facilitates an accurate diagnosis, enables patients to receive all needed examinations in due time, mediates the implementation and monitoring of optimal GDMT, patient education and self-empowerment, and structures the appropriate modus of follow-up including discussion of escalation or de-escalation of therapy.

In 2016, the German Cardiac Societies, Deutsche Gesellschaft für Kardiologie (DGK) and Deutsche Gesellschaft für Thorax-, Herz- und Gefäßchirurgie (DGTHG), have started an initiative to ensure fast and state-of-the-art diagnostics and treatment of *de novo* HF or acute decompensating chronic HF to reduce the number of rehospitalizations of these patients (Tschierschke et al., 2013, Ertl et al., 2016, Kreusser et al., 2018). For this purpose, physicians offering different levels of care can opt to undergo a certification procedure to acquire a Heart Failure Unit (HFU) certificate. Three types of HFUs exist: HFU Residential Cardiologist, HFU Focus Hospital, HFU Supraregional Center. The current status of the certification process can be viewed at: <https://hfu.dgk.org/zertifizierte-hfus/>. To develop optimal

efficiency, the DGK highly recommended that regionally certified HFUs join forces in so-called HFU Networks thus enabling a comprehensive patient care – from acute hospitalization to long-term care.

However, there are limited data available to describe the current status of quality of HF care, or to quantify the impact of quality-of-care improvement measures such as HFUs on outcomes among patients with HF. In particular, the impact of the new structure, i.e. HFUs with their HFU Networks, has not been assessed.

### **Research question and objectives**

The primary objective was to describe the quality of HF patient care utilizing the quality-of-care indicators (QI) suggested by the 2021 ESC HF Guideline McDonagh et al., 2021 (McDonagh et al., 2021) and Aktaa et al., 2022 (Aktaa et al., 2022) in HFU and non-HFU centers over a period of up to 6 months following a decompensation.

### **Study design**

This was a multicenter, non-randomized, non-interventional five-cohort study with prospective and retrospective collection of primary data on HFrEF patient care across different types of HFU or non-HFU centers across Germany, in which patients were followed for six months after experiencing a decompensation event.

### **Setting**

125 sites were planned, comprising five different structural settings with 25 sites in each:

- Cohort A consists of: Supra-regional HFU Centers and HFU Focus Hospitals
- Cohort B consists of: Non-HFU Hospitals
- Cohort C consists of: HFU Residential Cardiologists
- Cohort D consists of: Non-HFU Residential Cardiologists
- Cohort E consists of: General practitioners (GPs)

### **Subjects and study size, including dropouts**

A total of 1,250 patients (10 per each of the 125 sites) were planned for recruitment, all adults ( $\geq 18$  years) with diagnosed HFrEF and a recent decompensation event (within 3 months), eligible only if they provided informed consent, and not participating in another interventional study or unable to consent.

### **Variables and data sources**

Prospective and retrospective primary data collection from patient files and physician and discharge letters ("Arztbriefe") was performed without imposing a strict visit schedule on participants to avoid interference with routine clinical care.

Variables documented in this study include:

- Sociodemographic patient variables
- Clinical patient variables
- Study site characteristics
- Patient care characteristics
- Clinical outcome variables
- Specific indicators of quality of care

## Statistical methods

Only descriptive data analyses were carried out, supported by calculation of confidence intervals. All statistical analysis were performed in an explorative way.

## Results

A total of 899 patients were enrolled across 97 participating sites, representing five distinct cohorts. The largest patient group was recruited from supra-regional HFU centers and HFU focus hospitals (N=253, 28.1%), followed by non-HFU residential cardiologists (N=247, 27.5%), HFU residential cardiologists (N=183, 20.4%), GPs (N=120, 13.3%), and non-HFU hospitals (N=96, 10.7%).

The 97 sites included in the study comprised 23 (23.7%) HFU hospitals, 11 (11.3%) non-HFU hospitals, 20 (20.6%) HFU residential cardiologists, 25 (25.8%) non-HFU residential cardiologists, and 18 (18.6%) GPs. Structural analysis demonstrated marked heterogeneity across site types. Supra-regional HFU centers were the only sites reporting heart surgery capabilities (60.9%) and had the highest proportion of intensive care units (87.0%). Cardiological interventions were most frequently available in supra-regional HFU centers (87.0%), less commonly in non-HFU hospitals (54.5%), and less frequently in residential cardiology practices (40.0% HFU vs. 16.0% non-HFU); such interventions were not available at GP sites. In contrast, basic diagnostic infrastructure such as electrocardiogram (ECG) and sonography was widely available across all cohorts ( $\geq 72\%$ ). Personnel structures also varied considerably. Supra-regional HFU centers reported the largest physician teams (mean  $40.0 \pm 27.1$ ) and the highest average number of staff caring for HF patients ( $29.7 \pm 32.1$ ). HF nurses and specialized HF assistants were most frequently documented in HFU centers and HFU residential cardiology practices, whereas their presence was rare in GP settings. Multidisciplinary teams for HF management were consistently present in all cohorts except GPs, and education on HF self-care was reported across all site types, with differences in scope and intensity.

During the course of the study, 169 patients (18.8%) discontinued documentation prematurely. The most frequent reason for early termination was death (34.7%), followed by loss to follow-up (31.7%) and screening failure (22.2%). Death as the primary reason occurred most often in supra-regional HFU centers (49.1%), while loss to follow-up was more common among patients managed by residential cardiologists (44.8–47.1%). Screening failures were predominantly reported by non-HFU residential cardiologists (35.3%) and GPs (48.5%). Other reasons, such as patient decision, withdrawal of informed consent, or adverse events, were rare ( $<5\%$  overall).

Patient follow-up was high across all cohorts, with 82.7% documented at Month 3 and 85.0% at Month 6 (end of study). Follow-up rates were similar between the cohorts, ranging from approximately 79.9% to 90.2%. Regarding visit modality, two-thirds of follow-up visits were conducted on site (65.7%) and one-third by telephone (33.7%), with marked differences across cohorts: on-site visits were most frequent among GPs (92.1%) and least frequent in non-HFU hospitals (34.0%), where telephone documentation predominated.

The analysis set (AS) comprised 862 patients with a mean age of 71.4 years; patients treated by GPs were the oldest on average (75.8 years). Overall, 74.7% were male and 84.6% were Caucasian. Most patients were publicly insured (86.3%). A majority (75.8%) reported no care dependency, while 2.9% had severe impairment of independence. Educational attainment was generally low, with up to one-third reporting only junior high school (Hauptschule) as highest graduation in some cohorts. Completed professional training was documented in 44.8% of patients, while only 3.2% held a university degree. Most patients were not working (74.7%); 8.7% were unable to work, and among these, HFrEF was the reported cause in 41.3%. Retirement was common (66.6%), particularly among patients seen by GPs (79.8%).

At baseline (Visit 1), patients had a mean systolic/diastolic blood pressure of 124/77 mmHg, pulse of 80 bpm, and Body Mass Index (BMI) of  $28.2 \text{ kg/m}^2$ . At Visit 2, mean systolic/diastolic blood pressure was 122/74 mmHg, pulse decreased to 72 bpm, and BMI was  $27.6 \text{ kg/m}^2$ . At Visit 3, blood pressure remained stable at 124/75 mmHg, pulse was 73 bpm, and BMI was  $28.0 \text{ kg/m}^2$ .

At baseline, nearly all patients had at least one comorbidity, with the most frequent categories being cardiovascular (94.5%), metabolic (66.2%), and renal diseases (49.2%). The leading conditions were hypertension (72.5%), hyperlipidemia (52.2%), atrial fibrillation /atrial flutter (49.9%), ischaemic heart disease (46.2%), heart valve disease (45.0%), and chronic kidney disease (40.8%). During the study period, comorbidity patterns remained largely consistent. Overall, the comorbidity burden was high and broadly comparable across all cohorts.

At baseline, the mean left ventricular ejection fraction was 29.5% (range 10–40%) and improved over time to 38.2% at Visit 2 and 40.5% at Visit 3. n-terminal pro-B-type natriuretic peptide levels declined from a mean of 964.5 pmol/L at Visit 1 to 634.0 pmol/L at Visit 2 and 459.6 pmol/L at Visit 3, with higher values observed in patients treated at supra-regional HFU centers compared to outpatient settings. Renal function was impaired in a substantial proportion of patients: at baseline, nearly half had estimated glomerular filtration rate <60 mL/min/1.73m<sup>2</sup>, and similar proportions persisted through follow-up. Median serum creatinine levels remained relatively stable.

Across all study visits, the most frequently documented blood analyses were electrolytes, large blood count, and liver enzyme values (glutamic-oxaloacetic transaminase [GOT]/ glutamate pyruvate transaminase [GPT]), with thyroid-stimulating hormone (TSH) also frequently assessed at baseline. Documentation rates were highest in supra-regional HFU centers and non-HFU hospitals, while outpatient cohorts showed lower documentation frequencies. Documentation declined over time, with electrolytes measured in two-thirds at baseline but one-third at later visits.

The median time between HFrEF diagnosis and index date was 0.0 months overall, reflecting mainly first diagnosis at the index event. A majority of patients (63.0%) had at least one prior decompensation, typically occurring close to the index date. Most patients were classified as New York Heart Association (NYHA) III (52.4%), followed by NYHA II (27.8%), NYHA IV (10.1%), and NYHA I (3.1%). Left bundle branch block was present in 24.8%. Only a minority received device therapy: 7.7% were offered CRT and 12.9% were offered an ICD, with actual implantation rates of around 3% for both.

The median time from the index decompensation to baseline was 14 days overall, but shorter in hospital-based cohorts (6–7 days) compared with outpatient cohorts (21–27 days). Most patients (70.6%) were treated stationarily, with hospitalization rates ≥95.7% in hospitals versus 50.9% in residential cardiologists and GP cohorts.

Across all patients, ARNI/ACEi/ARB (93.8%) and BB (93.4%) were almost universally prescribed. MRAs were used in 74.2%, with lower uptake in non-HFU residential cardiologist and GP cohorts. SGLT2i were prescribed in 85.5% overall, but less often among GPs (66.0%). Loop diuretics were nearly universal (97.3%).

The primary endpoint, the opportunity-based QI, showed an overall mean score of  $0.631 \pm 0.144$  (median 0.667; range 0.143–1.000), indicating that on average about two-thirds of care standards were achieved across patients with LVEF ≤40%. Across cohorts, mean QI scores ranged from 0.593 in GPs to 0.653 in HFU residential cardiologists, with supra-regional HFU centers (0.642), non-HFU hospitals (0.618), and non-HFU residential cardiologists (0.621) falling in between.

Domain 1 – Structural framework: Only 22.7% of sites had a dedicated multidisciplinary HF team, with availability concentrated in supra-regional HFU centers (60.9%). HF education staff were reported in 54.6% of sites, most frequently in HFU cohorts.

Domain 2 – Patient assessment: ECG documentation was high (91.5%), natriuretic peptides measurement less consistent (66.1% overall, 88.8% in supra-regional HFU centers, 48.1% in GPs). Comprehensive lab profiles were rarely documented (7.7%). Referral to cardiac rehabilitation was infrequent (4.6%), while early follow-up within 4 weeks after hospitalization occurred in 34.0%.

Domain 3 – Initial treatment: Prescription rates for BB and ACEi/ARB/ARNI exceeded 95% in eligible patients. ARNI use was lower (≈75%), MRAs prescribed in about 80%, and SGLT2i in about 90%, with lowest uptake among GPs. Loop diuretics were nearly universal. Around 70% of patients received all four foundational therapies, highest in supra-regional HFU centers and lowest in GPs. Combined initiation of four therapies typically occurred within (median) 5 days in specialized settings but was

delayed in non-HFU and GP care. Across all cohorts, patients were covered for a median of 179 day with all four treatment classes.

Domain 4 – Therapy optimization: Only 30.3% of eligible patients received CRT, ranging from 0% in non-HFU hospitals and GPs to 50% in non-HFU residential cardiologists. ICD implantation for primary prevention was 24.7%, ranging from 20.5% in supra-regional HFU centers to 30.8% in non-HFU residential cardiologists.

Domain 5 – Assessment of (Health-Related Quality of Life) HRQoL: Only 3.7% of patients completed at least one HRQoL questionnaire. EuroQol-5 Dimension (EQ-5D) was most frequent (2.2%), Kansas City Cardiomyopathy Questionnaire (KCCQ) and other tools were rarely used (<1%).

Healthcare resource utilization: 69.5% of patients were not hospitalized, 20.8% had one admission, and 9.7% had multiple admissions, with recurrence higher in inpatient cohorts. Mean stay without Intensive Care Unit (ICU) was 7.1 days, longest among GP patients (10.3 days). ICU patients had longer stays (mean of 15.8 days). Cardiac interventions were performed in 114 patients, most often valve procedures (57.9%), followed by CRT-P/D (22.8%) and ICD implantation (21.1%).

## Discussion

The primary endpoint, the opportunity-based composite QI, showed that on average two-thirds of recommended care standards were achieved across all cohorts. Scores varied only modestly between cohorts, with lowest values in GPs and highest in HFU residential cardiologists. Overall, the findings indicate that partial but not complete adherence to the QIs as suggested by Aktaa et al., 2022 (Aktaa et al., 2022) was consistently observed across both HFU and non-HFU cohorts.

Structural and resource-related differences between HFU and non-HFU sites were pronounced. Dedicated multidisciplinary HF teams and specialized staff for education and self-care were concentrated in HFU centers, whereas such resources were scarce in non-HFU sites, particularly in GPs. This contrast in structural frameworks was also reflected in patient assessment: HFU centers more frequently documented NPs, comprehensive laboratory parameters, and early follow-up, whereas non-HFU sites demonstrated lower implementation of these quality measures.

In terms of initial pharmacological treatment, similarities outweighed differences. High prescription rates of ACEi/ARB/ARNI and BB were observed across all cohorts, while treatment with MRAs and SGLT2i was consistently lower in GPs. Initiation of all four therapies occurred earlier and more frequently in HFU cohorts, though persistence was maintained across settings. Thus, while the baseline implementation of pharmacotherapy was broadly consistent, HFU settings demonstrated advantages in completeness and timeliness of therapy.

Device therapy revealed clear differences, with low application across all cohorts but most restricted in non-HFU settings. CRT and ICD implantation were only documented in a minority of eligible patients, and in some non-HFU cohorts no implantations occurred.

Assessment of HRQoL was rarely performed in any setting, indicating no substantial differences across HFU and non-HFU cohorts in this domain.

Hospitalization rates during follow-up were low overall, though recurrent admissions were more frequent in inpatient cohorts compared with ambulatory care. Length of stay was longer for GP patients without ICU involvement, while ICU-treated patients experienced the longest admissions across settings. Cardiac interventions were more frequently performed in hospital-based HFU cohorts compared with non-HFU sites.

Taken together, the results demonstrate that the quality of care for HFrEF patients after decompensation was characterized by overall partial adherence to guideline-recommended standards across all settings, as assessed by the opportunity-based QIs (Aktaa et al., 2022). While structural and process-related differences were evident, particularly in specialized assessments, therapy optimization, and device use, pharmacological treatment was broadly implemented across both HFU and non-HFU cohorts.

**Conclusion**

The CONNECT study provides a comprehensive assessment of HF care quality in Germany using standardized ESC-HFA QIs (Aktaa et al., 2022, McDonagh et al., 2021). The results demonstrate moderate overall adherence to guideline-recommended care for patients with HFrEF following a decompensation event, with variability across different healthcare settings. Differences were observed between HFU and non-HFU centers, with more advanced structural resources, broader diagnostic assessments, and higher uptake of guideline-directed therapies in specialized settings, while several aspects of care such as device therapy and structured follow-up showed consistently low implementation across all cohorts. These findings support the feasibility of applying structured QIs in routine clinical practice and highlight opportunities for targeted quality improvement across all levels of care.

## 1 List of abbreviations

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ACEi	Angiotensin-Converting Enzyme Inhibitors
AF	Atrial Fibrillation
ARB	Angiotensin Receptor Blocker
ARNI	Angiotensin Receptor-Neprilysin Inhibitor
AS	Analysis Set
BB	Beta-Blockers
BMI	Body Mass Index
BNP	B-type Natriuretic Peptide
CCU	Critical Care Unit
CKD	Chronic Kidney Disease
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CRT	Cardiac Resynchronization Therapy
CRT-D	Cardiac Resynchronization Therapy with Defibrillator
CRT-P	Cardiac Resynchronization Therapy-Pacemaker
CV	Cardiovascular
DGK	Deutsche Gesellschaft für Kardiologie
DM	Diabetes Mellitus
ECG	Electrocardiogram
eGFR	Estimated Glomerular Filtration Rate
ER	Emergency Room
ESC	European Society of Cardiology
EQ-5D	EuroQol-5 Dimension
GDMT	Guideline-Directed Medical Therapy
GOT	Glutamic-Oxaloacetic Transaminase
GP	General practitioner
GPT	Glutamate Pyruvate Transaminase
HF	Heart Failure
HFA	Heart Failure Association
HFmrEF	Heart Failure with midrange Ejection Fraction
HFpEF	Heart Failure with preserved Ejection Fraction
HFrEF	Heart Failure with reduced Ejection Fraction
HFU	Heart Failure Unit
HRQoL	Health-Related Quality of Life
IA	Interim Analysis
ICD	Implantable Cardioverter Defibrillator
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IHD	Ischaemic Heart Disease
IRB	Institutional Review Board
KCCQ	Kansas City Cardiomyopathy Questionnaire
LBBB	Left Bundle Branch Block
Lp (a)	Lipoprotein (a)
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Regulatory Activities

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MRA	Mineralocorticoid Receptor Antagonists
NPs	Natriuretic Peptides
NTproBNP	N-Terminal pro-B-type Natriuretic Peptide
NYHA	New York Heart Association
OMT	Optimal medical therapy
QI	Quality Indicator
QoL	Quality of Life
SGLT2i	Sodium-Glucose co-Transporter 2 inhibitor
SmPC	Summaries of Product Characteristics
TSH	Thyroid-Stimulating Hormone

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