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# Dose matters! Optimisation of guideline adherence is associated with lower mortality in stable patients with chronic heart failure☆

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ABSTRACT

*Aims:* Guidelines have been published for improving management of chronic heart failure (CHF). We examined the association between improved guideline adherence and risk for all-cause death in patients with stable systolic HF.

*Methods:* Data on ambulatory patients (2006–2010) with CHF and reduced ejection fraction (HF-REF) from the Austrian Heart Failure Registry (HIR Austria) were analysed. One-year clinical data and long-term follow-up data until all-cause death or data censoring were available for 1014 patients (age 65 [55–73], male 75%, NYHA class I 14%, NYHA II 56%, NYHA III/IV 30%). A guideline adherence indicator (GAI [0–100%]) was calculated for each patient at baseline and after 12 ± 3 months that considered indications and contraindications for ACE-I/ARB, beta blockers, and MRA. Patients were considered ΔGAI-positive if GAI improved to or remained at high levels (≥80%). ΔGAI50+ positivity was ascribed to patients achieving a dose of ≥50% of suggested target dose.

*Results:* Improvements in GAI and GAI50+ were associated with significant improvements in NYHA class and NT-proBNP (1728 [740–3636] to 970 [405–2348]) ($p < 0.001$). Improvements in GAI50+, but not GAI, were independently predictive of lower mortality risk (HR 0.55 [95% CI 0.34–0.87; $p = 0.01$]) after adjustment for a large variety of baseline parameters and hospitalisation for heart failure during follow-up.

*Conclusions:* Improvement in guideline adherence with particular emphasis on dose escalation is associated with a decrease in long-term mortality in ambulatory HF-REF subjects surviving one year after registration.



## 1. Introduction

Chronic heart failure (CHF) is a major health problem and is associated with high morbidity and mortality. Angiotensin-converting enzyme inhibitors (ACE-I), angiotensin receptor II type-1 blockers (ARB), beta blockers (BB), and mineralocorticoid receptor antagonists (MRA) improve survival in patents with CHF [1]. Results of large placebo-controlled, randomised trials have been integrated into guidelines for the diagnosis and treatment of acute and chronic HF published and regularly updated by cardiologic societies [1,2]. Various registries and surveys have, however, consistently indicated that recommended medication is suboptimally used, whereby under-treatment may

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mean either under-use of recommended treatments [3–7] or prescription of low doses of these drugs [3,4,6]. More recent surveys have shown gradual progress in both, but the number of patients treated with trial-mandated doses has remained low [4,8–14]. Efficacy of guideline adherence in terms of reduction in cardiovascular hospitalisations and all-cause mortality has been shown in various cohorts with stable [11,13,15] and unstable HF [11] and also in heart failure with preserved ejection fraction (HF-PEF) [11]. No information is available on the efficacy of active optimisation of guideline adherence in CHF. In particular, the role of dose adjustment has not yet been addressed.

To specifically assess these issues we analysed data from the Austrian Heart Failure Registry (HIR Austria), which recruits patients from outpatient clinics and cardiologists in private practice. Two principal questions were addressed: i) Does guideline adherence improve over time, in particular with regard to dose increase, and what are its determinants? ii) How does improved guideline adherence impact mortality risk in patients with CHF and reduced systolic function?

## 2. Methods

### 2.1. Study design, patients and measurements

The principles of HIR Austria have been published previously [16]. HIR Austria is a prospective, multicentre, observational registry of patients presenting in heart failure outpatient clinics (HFCs) in primary, secondary and tertiary referral centres and in the offices of cardiologists in private practice in Austria. These facilities offer their services at no cost to patients with social insurance, which covers practically the entire population of Austria. Patients are referred by general practitioners, internists and hospital departments of cardiology and internal medicine. The HFCs' main focus comprises initiation of evidence-based pharmacotherapy, up-titration to target doses or maximal tolerable doses, patient education and introduction of tailored diagnostic procedures and non-pharmacologic therapies. The clinics work according to prevailing ESC guidelines. Performance of the participating HFCs is monitored by annual reports benchmarking key parameters, such as the proportion of patients treated with RAS inhibitors and beta-blockers in the individual clinics. Patients were recruited from June 2006 to June 2010. Eligible patients were ≥18 years of age. The diagnosis of CHF was based on the presence of current or previous symptoms or characteristic clinical signs such as dyspnoea, oedema or pulmonary crepitations, and evidence of left ventricular dysfunction. Patients were included irrespective of the underlying cause of heart failure. Heart failure with reduced ejection fraction (HF-REF) was defined as a left ventricular ejection fraction (LV-EF) of 40% or less as measured by two-dimensional echocardiography at study entry. Medical history, laboratory parameters and medication were collected at baseline and a predefined follow-up visit 12 ± 3 months thereafter. Intensity of medical supervision and adaptation of heart failure therapy from baseline to follow-up were at the discretion of the treating physician. Patients were followed until December 2011 (time of data censoring) or until death. Death events were retrieved from the Austrian Mortality Registry. No patient was lost to long-term follow-up.

Anaemia was defined as haemoglobin levels <12 mg/dl for women and <13 mg/dl for men. The estimated glomerular filtration rate (eGFR) was calculated according to the MDRD formula [17]. Patients gave written informed consent for data collection. The study complied with the principles outlined in the Declaration of Helsinki and was approved by a central ethics committee.

### 2.2. Calculation of the pharmacological guideline adherence indicator (GAI)

The guidelines for diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology 2008 were used [18]. Quality of pharmacotherapy was assessed at baseline and one-year follow-up by calculating GAI (0–100%) as the number of drugs taken divided by the number of drugs indicated multiplied by 100 [15]. For both time-points, GAI was computed as described by Störk et al. [11]. GAI considered ACE-I/ARB, BB and MRA as the only substance classes with strong evidence for improving outcome. Also, the following indications and contraindications were incorporated: a) patients in NYHA functional class I were included who required ACE-I or ARB, and BB post-myocardial infarction; b) patients in NYHA III/IV and post-myocardial infarction were included who required MRA; c) bradycardia <50 beats per minute and systolic blood pressure (SBP) <90 mm Hg were considered contraindications for BB; d) SBP <90 mm Hg, eGFR <30 ml/min per 1.73 $m^2$ and serum potassium >5.5 were considered contraindications for ACE-I/ARB and MRA.

The algorithms employed for computation of GAI and GAI50+ were as follows:

ACE inhibitor/ARB: If "NO" to diagnosis of eGFR ≤ml/min per 1.73 $m^2$ AND SBP ≥90 mm Hg AND potassium ≤5.5 mmol/L, THEN guidelines apply.

Beta-blockers: If NYHA class II–IV OR previous myocardial infarction AND SBP ≥90 mm Hg AND heart rate ≥50/min, THEN guidelines apply.

Mineralocorticoid receptor antagonists: If NYHA class III/IV OR previous myocardial infarction AND if "NO" to diagnosis of eGFR ≤30 ml/min per1.73 $m^2$ AND potassium ≤ 5.5 mmol/L AND, THEN guidelines apply.

GAI 0–49% was considered low, 50–79% medium, and 80–100% high. In addition to GAI, a second version of GAI (GAI50+) was calculated that took into account not only appropriate administration of the respective substance class (ACE-I/ARB, BB, MRA), but also administration of at least 50% of the guideline-recommended target dose for ACE-I/ARB and BB at one-year follow-up. Changes in GAI and GAI50+ from baseline to one-year follow-up (ΔGAI, ΔGAI50+, respectively) were considered positive if GAI improved to or remained at a high level (≥80%) during follow-up. ΔGAI50+ positivity refers to a final equivalent dose ≥50% in both substance classes.

### 2.3. Statistical analysis

Data are presented as mean ± standard deviation, median (25th, 75th percentile), or number (%), as appropriate. Groups were compared using the *t* test, Mann-Whitney *U* test, and chi-square or Fisher's exact test, as appropriate. When comparing the quality of pharmacotherapy at baseline and follow-up, GAI50+ was used as an ordinal variable. Determinants of inadequate optimisation of dose-related guideline adherence were sought by multivariable logistic regression including significantly different baseline characteristics, co-morbidities and interim hospitalisation for worsening heart failure. Odds ratios (OR) with respective 95% confidence intervals (CI) are reported. Age and sex were forced into all models. Sex-stratified Cox proportional hazards regression was applied to estimate the association between GAI, GAI50+ (used as indicator variables rather than continuous variables) and the respective changes over time (ΔGAI and ΔGAI50+) and time to all-cause death; hazard ratios (HR) with 95% CI are reported. Variables for the uni- and multivariable Cox proportional hazards regression analysis were selected based on differences in baseline characteristics between ΔGAI-positive and -negative patients. Since progressive deterioration and anticipated death might have influenced optimisation of guideline adherence, uni- and multivariable Cox regression were also calculated with a lag-time of six months after one-year follow-up.

P values <0.05 were considered to indicate statistical significance. Statistical analysis was performed using the SPSS software package (SPSS 17.0 for Windows, SPSS Corp.).

## 3. Results

From June 2006 to June 2010 2824 patients were recruited for HIR Austria. Of these 1751 (62%) were diagnosed with HF-REF. A complete dataset of the HF-REF cohort at one-year follow-up (355 ± 3 days) when ΔGAI and ΔGAI50+ were calculated and for a subsequent monitoring period of at least six months at time of data censoring in December 2011 were available for 1014 patients. Important baseline characteristics are summarized in Table 1. Of the study patients 25% were female, and ischemia was the leading cause of heart failure. In 9% the leading cause was not identified.

### 3.1. Baseline

#### 3.1.1. Drug and device therapy

Of the patients 90.5% were treated with ACE-I and/or ARB, 87.8% with BB, and 42.7% with MRA (Fig. 1a and b). Treatment with diuretics (74.1%), digoxin (18.6%), amiodarone (11.7%), and oral anticoagulation (36.2%) is also depicted in Fig. 1. Fig. 2 shows the percentages of patients with ACE-I/ARB and BB, who were on target dose and on ≥50% of target dose of the respective medication. An implantable cardioverter defibrillator (ICD) was implanted in 136 (13.4%) patients, cardiac resynchronisation therapy (CRT) in 57 (5.6%) patients (Fig. 1).

#### 3.1.2. Guideline adherence

Overall quality of guideline adherence for GAI and GAI50+ is shown in Fig. 3. As compared to patients with a high GAI50+, patients with a low GAI50+ were characterized by older age (66 [55–75] vs. 64 [54–71]; $p < 0.001$), higher NYHA class ($p < 0.001$), higher percentage of ischemic CMP [19] (43% vs. 26%; $p < 0.001$), lower percentage of arterial hypertension (55% vs. 67%; $p < 0.001$), lower eGFR (68 [50–96] vs. 77 [55–103]; $p = 0.022$) and serum potassium 4.3 [3.9–4.7] vs. 4.4 [4.1–4.8]; $p < 0.001$). By contrast, no between-group differences were seen for gender, HF duration, co-morbidities such as COPD, diabetes, anaemia, or for NT-proBNP.

**Table 1**
Baseline characteristics of the overall study cohort and subgroups of patients with and without improvement in dose-related guideline adherence (ΔGAI50+ negative and positive). Positivity was assumed if adherence improved to or remained at a high level (≥80%) with ≥50% of the target dose for ACE-I/ARB and BB at one-year follow-up. Data for 1,014 patients are reported as number (percentage) or median (interquartile range). Data on NT-proBNP were available for 818 patients. For all other variables, <5% of data was missing.

| | All patients | ΔGAI50+ negative | ΔGAI50+ positive | p |
|---|---|---|---|---|
| | n = 1014 | n = 361 | n = 653 | |
| Age, years | 65 (55–74) | 68 (59–75) | 63 (53–71) | <0.001 |
| Female sex, % | 27.4 | 24.8 | 24.8 | 0.995 |
| Number of hospital admissions within the last 12 months before first visit | 1.06 ± 1.11 | 1.24 ± 1.36 | 1.02 ± 1.02 | 0.041 |
| Duration of heart failure > 6 months, % | 61.1 | 68.7 | 55.3 | <0.001 |
| *Underlying cause of heart failure* | | | | <0.001 |
| Ischaemic, % | 35.5 | 50.1 | 31.6 | |
| Dilated, % | 24.6 | 21.5 | 30.4 | |
| Hypertensive, % | 9.5 | 5.5 | 11.3 | |
| Valvular, % | 3.3 | 2.6 | 2.4 | |
| Inflammatory, % | 5.0 | 2.4 | 7.0 | |
| Other, % | 10.3 | 5.3 | 10.9 | |
| Unknown, % | 11.8 | 12.6 | 6.4 | |
| NYHA class, % | | | | |
| I | 17.0 | 7.5 | 17.7 | 0.003 |
| II | 57.7 | 60.9 | 54.0 | |
| III | 24.0 | 29.6 | 26.7 | |
| IV | 1.3 | 2.0 | 1.6 | |
| Left ventricular ejection fraction | | | | 0.436 |
| 30–39% | 47.0 | 48.7 | 46.1 | |
| <30% | 53.0 | 51.3 | 53.9 | |
| *Co-morbidity* | | | | |
| Coronary artery bypass graft, % | 9.4 | 13.6 | 8.6 | 0.015 |
| Percutaneous coronary angioplasty, % | 28.2 | 40.5 | 22.9 | <0.001 |
| Myocardial infarction, % | 31.3 | 52.2 | 23.8 | <0.001 |
| Atrial fibrillation, % | 34.2 | 35.0 | 31.3 | 0.248 |
| Implantable cardioverter defibrillator, % | 11.3 | 14.4 | 12.9 | 0.388 |
| Cardiac resynchronization therapy, % | 5.0 | 5.5 | 5.7 | 0.940 |
| Hypertension, % | 62.4 | 62.8 | 60.9 | 0.560 |
| Diabetes, % | 28.1 | 31.4 | 28.0 | 0.269 |
| Chronic obstructive lung disease or asthma, % | 23.3 | 23.3 | 22.3 | 0.719 |
| Anaemia, % | 23.0 | 26.3 | 20.9 | 0.066 |
| Renal insufficiency, GFR <60 ml/min per 1.73 $m^2$, % | 32.6 | 42.1 | 26.2 | <0.001 |
| Obesity, % (=BMI >30) | 23.2 | 21.6 | 24.6 | 0.286 |
| *Anthropometric, haemodynamic and laboratory parameters* | | | | |
| Systolic blood pressure, mm Hg | 128 (116–141) | 122 (112–137) | 128 (115–144) | 0.005 |
| Heart rate, 1/min | 73 (64–83) | 73 (63–83) | 73 (65–85) | 0.239 |
| Serum sodium, mmol/l | 140 (138–142) | 140 (138–143) | 140 (138–142) | 0.108 |
| Serum potassium, mmol/l | 4.4 (4.1–4.7) | 4.3 (4.0–4.7) | 4.4 (4.1–4.7) | 0.050 |
| Estimated glomerular filtration rate, ml/min/1,73 $m^2$ | 74 (54–99) | 65 (50–85) | 80 (58–104) | <0.001 |
| C-reactive protein, mg/dl | 0.3 (0.1–1.0) | 0.3 (0.1–0.9) | 0.4 (0.1–1.9) | 0.002 |
| Total cholesterol, mg/dl | 177 (149–210) | 172 (145–203) | 178 (149–212) | 0.034 |
| NT-proBNP, ng/l | 1450 (622–3232) | 1763 (753–3893) | 1699 (734–3570) | 0.577 |

GFR, glomerular filtration rate; BMI, body mass index; NT-proBNP, N-terminal brain natriuretic peptide.

### 3.2. One-year follow-up

#### 3.2.1. Changes in pharmacotherapy

Percentages of patients on various drug categories at one-year follow-up are shown in Fig. 1. Compared to baseline the use of ACE-I was not different after one year (72.8 vs. 69.2%), whereas ARB prescription markedly increased (19.6% vs. 27.5%), resulting in no difference in ACE-I/ARB use at one-year FU (90.5 vs. 92.1%). The proportion of patients on BB increased over time (87.8% vs. 91.6%). Prescription of MRAs (42.7% vs. 38.9%) and diuretics declined (74.1% vs. 68.9%) over time, and prescription of anticoagulation therapy increased modestly (36.2% vs. 39.1%).

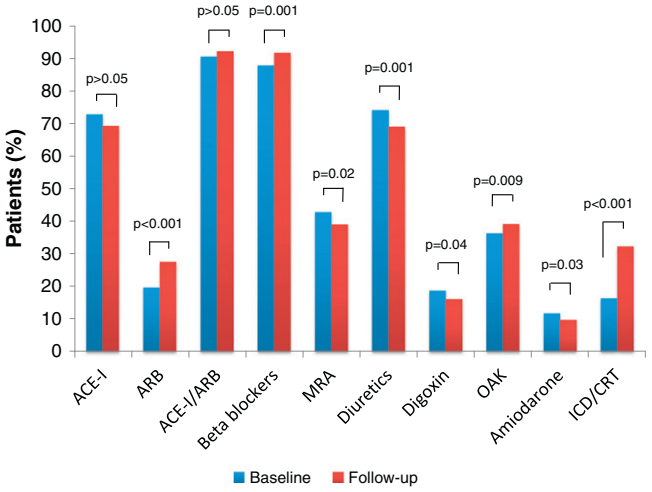
Changes in dosage of ACE-I/ARB and BB are shown in Fig. 2. The percentage of patients on target dose as well as on ≥50% of target dose increased significantly over time for all substances (p for delta <0.001). Notably, BB dosages were lowest at baseline and at follow-up. More patients were implanted with an ICD (n = 269 [26.5%]) or CRT (n = 144 [14.2]) at follow-up than at baseline (p for delta <0.001) (Fig. 1).

Changes in therapy were paralleled by a significant improvement in NYHA class (Fig. 4) and a decrease in NT-proBNP (970 [405–2348] vs. 1728 [740–3636]; p < 0.001). The number of hospital admissions for worsening HF between baseline and one-year follow-up was 1.1 ± 1.1.

#### 3.2.2. Changes in guideline adherence and its determinants

Changes in guideline adherence (ΔGAI) and dose-adjusted guideline adherence (ΔGAI50+) from baseline to one-year follow-up are shown in Fig. 3. ΔGAI+ was deemed positive (GAI improved to or remained at a high level [≥80%] during follow-up) in 75.7% and ΔGAI50+ in 64.4% of patients. Important baseline characteristics of patients with ΔGAI50+ positive versus negative are summarized in Table 1. Patients who were not optimised with drug therapy were older, had a longer history of heart failure and were more likely to be in a higher NYHA class. Also, ischemic heart failure and impaired renal function were significantly more prevalent and number of hospital admissions for HF during one-year follow-up was higher (1.3 ± 1.6 vs. 0.9 ± 1.5; p < 0.001). Determinants of a failure to improve GAI50+ as assessed by multivariable logistic regression analysis were (ordered by strength of association): interim hospitalisation for worsening HF (OR 2.00 [1.38–2.88]), ischemic aetiology (OR 2.0 [1.38–2.90]), eGFR per ln unit decrease (OR 2.37 [1.36–4.14]), age per decade (OR 1.3 [1.07–1.48]), NT-proBNP per ln unit increase (OR 0.77 [0.65–0.91]), and systolic BP per mm Hg increase (OR 0.99 [0.98–0.99]). Of note, neither gender, co-morbidities such as COPD, diabetes or anaemia, nor heart rate were associated with a failure to improve GAI50+.

a




b

| Medication at baseline (%) | |
|---|---|
| **ACE-I / ARB** | **90.5** |
| Enalapril | 13.5 |
| Lisinopril | 36.6 |
| Ramipril | 25.0 |
| other | 3.2 |
| Candesartan | 3.1 |
| Losartan | 11.9 |
| Valsartan | 3.9 |
| other | 2.8 |
| **ACE-I and ARB** | **2.3** |
| **Beta blocker** | **87.8** |
| Bisoprolol | 42.4 |
| Carvedilol | 31.7 |
| Metoprolol succinate | 14.4 |
| Nebivolol | 11.0 |
| other | 0.5 |
| **MRA** | **42.7** |
| Spironolactone | 90.4 |
| Eplerenone | 9.6 |

**Fig. 1.** a: Use of pharmacotherapy at baseline and one-year follow-up. ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor II type-1 blocker; MRA, mineralocorticoid receptor antagonist; OAK, oral anticoagulant therapy. b: Use of various ACE-I/ARB, beta blocker, and MRA substances at baseline (% of patients in the entire study cohort).

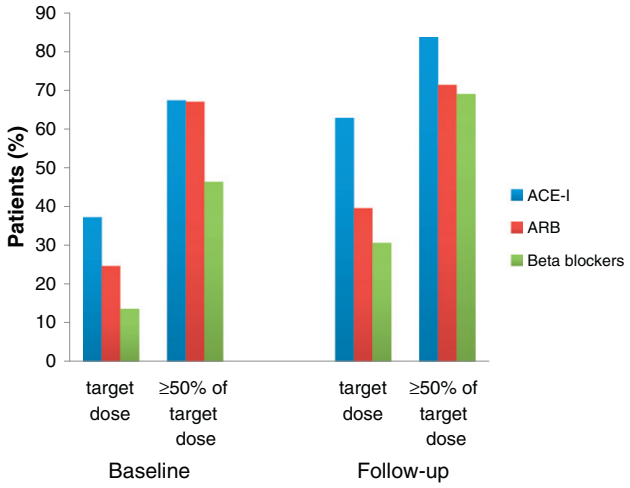



**Fig. 2.** Percentage of patients with ACE-I, ARB and beta blockers at target dose and ≥50% of target dose at baseline and one-year follow-up. Improvements from baseline to one-year follow-up were significant for all substances (p for delta < 0.001). ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor II type-1 blocker.

### 3.3. Effect of guideline adherence on mortality risk

Long-term follow-up for all patients until all-cause death or data censoring was 2.8 (1.8–4.4) years (2.7 [1.6–4.3] years in survivors vs. 2.4 [1.6–3.2] years in non-survivors). Mortality rate was 13.6 per 100 person-years of follow-up. In univariate, sex-stratified Cox regression analysis neither GAI nor GAI50+ at baseline was associated with a lower mortality risk.

Uni- and multivariable predictors of mortality risk are shown in Table 2. Age per year, NYHA class III/IV and hospitalisation for worsening HF during one-year follow-up were independently predictive for all-cause mortality. Improvements in guideline adherence were associated with lower mortality when dose escalation was considered (ΔGAI50+) (Fig. 5). By contrast, improvements in pharmacotherapy irrespective of dose (ΔGAI) were not predictive in the multivariable model (Table 2).

When lag-time analysis was applied to the uni- and multivariable Cox regression models, results were seen to be comparable (data not shown).

## 4. Discussion

Using a large prospective, longitudinal multi-site registry of patients with stable HF and reduced ejection fraction we sought to determine how optimisation of guideline adherence over the course of one year affects long-term outcome.

Our main findings were as follows: (i) Optimisation of guideline adherence was paralleled by a decrease in disease severity and resulted in a significant reduction in all-cause mortality risk. (ii) The survival benefit was seen to be independent of relevant baseline variables known to impact outcome and interim hospitalisation for worsening HF when dose escalation of ACE-I/ARB and BB was considered. (iii) Interim hospitalisation for worsening HF, ischemic CMP, renal

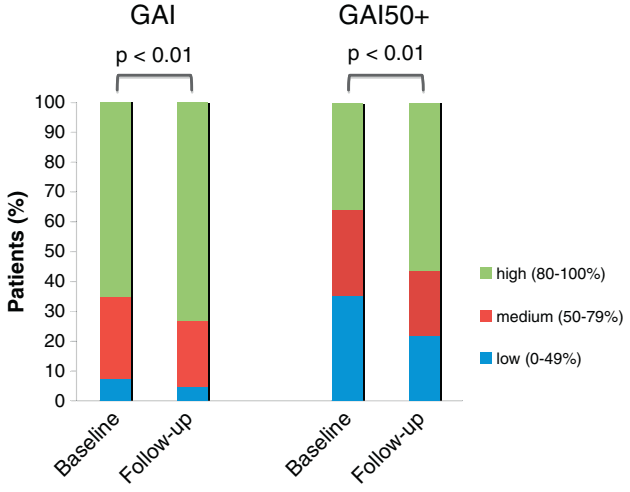



**Fig. 3.** Quality of guideline adherence indicator (GAI) and dose-adjusted guideline adherence indicator (GAI50+) at baseline and one-year follow-up.

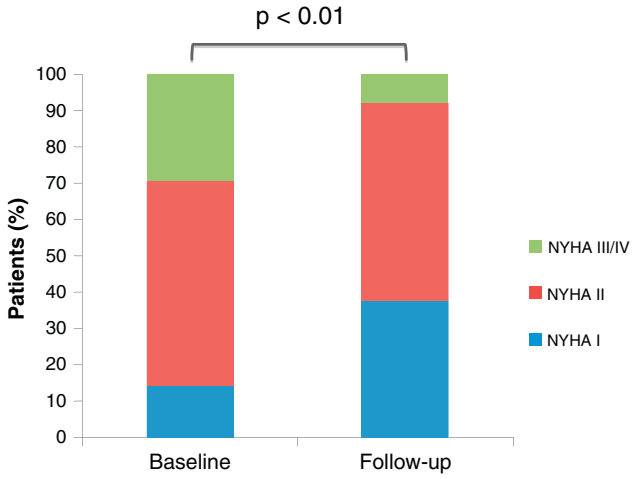



**Fig. 4.** Improvement in dose-related guideline adherence from baseline to one-year follow-up (ΔGAI50+) was paralleled by a significant improvement in NYHA class.

impairment, and older age were associated with the reluctance of treating physicians to improve guideline adherence over time, whereas higher NT-proBNP and higher systolic blood pressure at baseline favoured an improvement in therapy.

Results of previous surveys in various cohorts of stable and unstable HF indicated the efficacy of guideline-adjusted therapy in terms of reduced cardiovascular hospitalisation and all-cause mortality. These surveys were based on the assessment of treatment at a static point in time [11,15] or on temporal trends in medication [13]. Our study adds to the existing knowledge, because it demonstrated the importance of a dynamic improvement in guideline adherence over time in individual patients with CHF and reduced ejection fraction. A decrease in HF severity and a survival benefit were evident when prescription of neurohormonal therapy was gradually improved under consideration of advocated indications and contraindications and when the final dose approached the recommended target dose. Notably, the positive effect of improvements in dose-related guideline adherence on long-term survival was independent of various baseline characteristics such as age, severity and aetiology of HF, renal function, NT-proBNP levels, ICD/CRT implantation and interim hospitalisation for worsening HF. The survival benefit in patients with optimised therapy remained significant, even when a lag-time of six months after one-year follow-up was taken into consideration as a means of adjusting for a potential reluctance of physicians to improve medication in patients with progressive deterioration or for discontinuation of medication in anticipation of death.

In contrast to previous reports, quality of guideline adherence at baseline was not predictive for outcome. Most likely this can be attributed to the fact that patients in our cohort were less severely ill than, for example, those in the study by Störk et al. [11] since patients were recruited exclusively from outpatient clinics and cardiologists in private practice and, by definition, must have survived the first year after recruitment. Accordingly, the mortality rate was low in this population.

Guideline adherence at baseline in this Austrian cohort with unrestricted access to heart failure clinics and medication was higher by trend than in contemporaneously comprised European cohorts [4,11–13] or in a large, multicenter registry of chronic heart failure patients in North America [9]. For example, in the French IMPACT RECO survey 61% of patients received a combination of BB and ACE-I/ARB. In the ESC-HF pilot the number of patients on ACE-I, BB, and MRA was 35%, and distribution of GAI categories (low/medium/high) in a German cohort was 30%, 32%, and 38%, respectively. By contrast, the number of patients in our cohort treated with appropriate doses at baseline was comparably low [4,12,13]. Accordingly, improvement of guideline adherence over time was mostly achieved by dose escalation. Higher baseline levels of medication may explain why absolute and relative escalations in the prescription of ACE-I/ARB and BB in our cohort were lower than in the recently published longitudinal cohort of the IMPROVE-HF study [20].

Optimisation of dose-related guideline adherence during one-year follow-up was hampered by several factors. Intuitively, one would expect interim hospitalisation for heart failure to result in improved therapy. Since no information is available on patients' therapy at time of hospital admission, it remains speculative whether lack of optimised therapy is the cause rather than the consequence of worsening HF in these patients. The finding that patients with ischemic cardiomyopathy were less likely to receive guideline-adherent pharmacotherapy is in line with previous studies [11,13] and can mostly be attributed to inadequate prescription of MRAs in these patients. In fact, the percentage of patients in our cohort treated with MRAs even declined over time as opposed to the IMPROVE-HF study [20]. Interestingly, gender and comorbidities did not substantially impact prescription patterns. Clearly, our data should encourage reluctant physicians to proactively optimise heart failure therapy, particularly in patients with repeat hospitalisations for heart failure, ischemic cardiomyopathy and in the elderly.

Rates of ICD and CRT implantation at baseline were strikingly low. These rates increased during follow-up, but were still lower than in

**Table 2**
Uni- and multivariate predictors of all-cause mortality.

| | Univariate | | | | Multivariate | | | |
|---|---|---|---|---|---|---|---|---|
| | Wald | HR | 95% CI | P | Wald | HR | 95% CI | P |
| Age, per decade | 36.0 | 1.67 | 1.41–1.98 | <0.001 | 4.5 | 1.34 | 1.02–1.76 | 0.035 |
| NYHA class II vs. I | 9.4 | 4.85 | 1.77–13.30 | 0.002 | 2.0 | 2.83 | 0.68–11.81 | 0.155 |
| III/IV vs. I | 16.7 | 8.27 | 3.00–22.81 | <0.001 | 4.8 | 5.00 | 1.18–21.17 | 0.029 |
| Ischemic heart failure | 14.0 | 1.96 | 1.38–2.79 | <0.001 | 0.1 | 1.08 | 0.66–1.78 | 0.754 |
| Hypertension | 0.5 | 1.14 | 0.79–1.65 | 0.473 | 0.4 | 1.17 | 0.72–1.89 | 0.526 |
| Anaemia | 15.1 | 2.13 | 1.46–3.12 | <0.001 | 0.4 | 0.83 | 0.48–1.44 | 0.505 |
| Diabetes | 14.8 | 1.99 | 1.40–2.82 | <0.001 | 1.7 | 1.37 | 0.85–2.20 | 0.193 |
| Atrial fibrillation | 1.8 | 1.29 | 0.89–1.86 | 0.174 | 0.1 | 1.07 | 0.66–1.74 | 0.782 |
| Body mass index, per kg/m$^2$ | 0.9 | 0.98 | 0.95–1.02 | 0.353 | 4.3 | 1.04 | 1.00–1.07 | 0.038 |
| Interim hospitalisation for heart failure | 27.7 | 3.00 | 1.99–4.52 | <0.001 | 7.5 | 2.23 | 1.25–3.95 | 0.006 |
| eGFR, per ln decrease | 34.7 | 2.73 | 1.95–3.80 | <0.001 | 3.3 | 1.85 | 0.95–3.60 | 0.069 |
| NT-proBNP, per ln increase | 22.2 | 1.50 | 1.27–1.77 | <0.001 | 2.7 | 1.21 | 0.96–1.53 | 0.102 |
| ICD/CRT at baseline | 0.5 | 0.82 | 0.49–1.39 | 0.469 | 0.3 | 1.21 | 0.62–2.39 | 0.577 |
| *A) ΔGAI positive* | 8.5 | 0.57 | 0.39–0.83 | 0.003 | 1.7 | 0.71 | 0.43–1.19 | 0.194 |
| *B) ΔGAI50+ positive* | 22.06 | 0.44 | 0.31–0.62 | <0.001 | 5.7 | 0.55 | 0.34–0.90 | 0.017 |

eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal brain natriuretic peptide; ΔGAI positive, improvement in the guideline adherence indicator from baseline to one-year follow-up – see text; ΔGAI50+, improvement in the guideline adherence indicator from baseline to one-year follow-up with a final dosage of ≥50% for ACE-I/ARB and BB — see text.

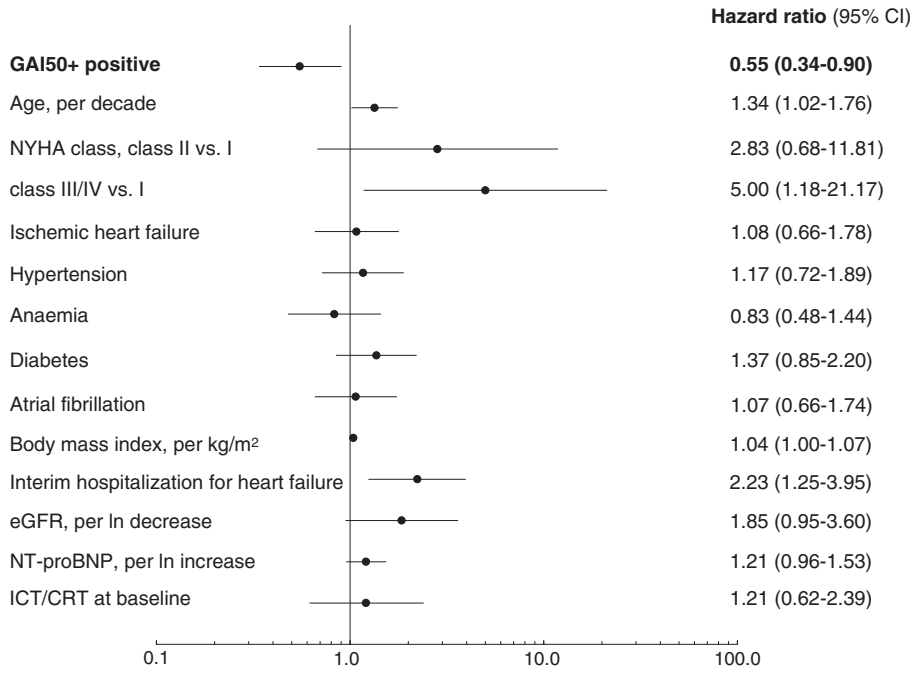



**Fig. 5.** Multivariable sex-stratified Cox regression analysis for all-cause mortality. Hazard ratios and 95% confidence intervals are shown in a forest plot. NYHA, New York Heart Association; eGFR, estimated glomerular filtration rate; NT-proBNP, amino-terminal pro-B-type natriuretic peptide.

recently published surveys [12,13,20–22]. Thus, there is still considerable room for improvement.

## 5. Limitations

Owing to its nature as an observational study, our findings can show only associations, but cannot prove causal relationships. Future, adequately designed studies are needed to confirm our hypothesis. Also, mean age in this cohort was lower than in the general CHF population and female gender is not adequately represented. Results are derived from a cohort of patients with stable HF. The mortality rate was low. Generalisation of our findings is therefore limited. Whether our findings can also be applied to sicker patients and/or to those whose therapy is optimised more quickly remains unclear. Information on guideline adherence refers to physicians' medication prescriptions. No information is available on patient adherence to prescriptions. Also, the reasons why treating physicians did not optimise pharmacotherapy in some patients during the follow-up period are not explicitly known. Data are derived from a non-monitored registry, which may limit data quality.

## 6. Conclusions

Our findings show that improvement in guideline adherence with particular emphasis on dose escalation is associated with a decrease in mortality risk in HF-REF subjects surviving for at least one year after registration. These hypothesis-generating results support the importance of vigorous improvement of neurohormonal therapy and the need for gradual dose escalation, which is frequently neglected in these patients. A prospective trial of this strategy would seem warranted.

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