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RESEARCH ARTICLE

Physicians' guideline adherence is associated with long-term heart failure mortality in outpatients with heart failure with reduced ejection fraction: the QUALIFY international registry

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Background Physicians' adherence to guideline-recommended therapy is associated with short-term clinical outcomes in heart failure (HF) with reduced ejection fraction (HFrEF). However, its impact on longer-term outcomes is poorly documented. Here, we present results from the 18-month follow-up of the QUALIFY registry.

Methods and results Data at 18 months were available for 6118 ambulatory HFrEF patients from this international prospective observational survey. Adherence was measured as a continuous variable, ranging from 0 to 1, and was assessed for five classes of recommended HF medications and dosages. Most deaths were cardiovascular (CV) (228/394) and HF-related (191/394) and the same was true for unplanned hospitalizations (1175 CV and 861 HF-related hospitalizations, out of a total of 1541). According to univariable analysis, CV and HF deaths were significantly associated with physician adherence to guidelines. In multivariable analysis, HF death was associated with adherence level [subdistribution hazard ratio (SHR) 0.93, 95% confidence interval (CI) 0.87–0.99 per 0.1 unit adherence level increase; $P = 0.034$] as was composite of HF hospitalization or CV death (SHR 0.97, 95% CI 0.94–0.99 per 0.1 unit adherence level increase; $P = 0.043$), whereas unplanned all-cause, CV or HF hospitalizations were not (all-cause: SHR 0.99, 95% CI 0.9–1.02; CV: SHR 0.98, 95% CI 0.96–1.01; and HF: SHR 0.99, 95% CI 0.96–1.02 per 0.1 unit change in adherence score; $P = 0.52$, $P = 0.2$, and $P = 0.4$, respectively).

Conclusion These results suggest that physicians' adherence to guideline-recommended HF therapies is associated with improved outcomes in HFrEF. Practical strategies should be established to improve physicians' adherence to guidelines.

Keywords Heart failure • Guidelines • Adherence • Medication • Dosage • Outcomes

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The complete list of the QUALIFY Committees and Investigators is provided in the online supplementary *Appendix S1*.

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Introduction

Heart failure (HF) is a major cause of mortality, morbidity and impaired quality of life and places a substantial financial burden on healthcare systems worldwide.[1–4] International guidelines make clear recommendations as to which evidence-based drugs should be prescribed for patients with HF with reduced ejection fraction (HFrEF).[5,6] However, observational studies have repeatedly shown that patients are missing out on potentially life-saving therapies.[7–10] Even when prescription rates of guideline-based HF medication are high, patients frequently fail to reach target doses (TDs)[11] and some, but not all, randomized studies have shown that suboptimal dosing may adversely influence outcomes.[12,13]

Although there is evidence that good adherence to HF treatment guidelines is associated with better short-term cardiovascular (CV) mortality[14] and hospitalization,[14,15] international data on the longer-term association of adherence to guidelines with clinical outcomes are scarce. Two recent publications suggest that initiation and continuation of angiotensin-converting enzyme inhibitors (ACEIs) and beta-blockers (BBs) reduced 1-year mortality but not readmission rates in a North American and in a Japanese population.[16,17]

To address the need for a longer-term, global perspective, the QUALIFY (QUality of Adherence to guideline recommendations for LIFe-saving treatment in heart failure surveY) study was established. It assessed adherence to five classes of medications recommended for HFrEF by the 2012 European Society of Cardiology (ESC) guidelines: ACEIs/angiotensin receptor blockers (ARBs), BBs, mineralocorticoid receptor antagonists (MRAs) and ivabradine,[18] in a large population recruited in Europe, the Middle East, Asia, Australia and the Americas. Previous reports have presented baseline characteristics and guideline adherence scores (good, moderate, poor) for the study population at enrolment,[19] and shown the beneficial impact of physicians' adherence to these five guideline-recommended classes of HF medication, including prescription of recommended doses, on clinical outcomes at 6-month follow-up.[20] In the current paper, we assessed the longer-term association of physicians' adherence with clinical outcomes, including mortality and unplanned hospitalizations, at 18-month follow-up.

Methods

QUALIFY is an international, prospective, observational, longitudinal survey of physicians' adherence to guideline-recommended medication for patients with HFrEF. Details of the study design, baseline evaluation and data management have been published previously.[19] Participating physicians at 549 centres in 36 countries reported data on adult outpatients (> 18 years old) with chronic HFrEF with reduced left ventricular ejection fraction (LVEF ≤ 40% on the most recent echocardiogram within 2 years of enrolment). Diagnosis was according to the clinical judgement of participating investigators, and all patients had been hospitalized for worsening HF within the previous 1–15 months. HF hospitalization was defined as an overnight stay in a hospital facility, driven by HF symptom deterioration.

For this analysis, we assessed the relationship between adherence at baseline and clinical outcomes (including all-cause mortality, CV death, HF death, unplanned CV hospitalization, unplanned HF hospitalization, and the composite of hospitalization attributable to HF or death attributable to CV death) at 18 months of follow-up. By definition, unplanned CV hospitalization included unplanned HF hospitalization. Events were reported by investigators and, as in many observational studies, there was no central adjudication of events, but formal guidance and training were provided to investigators to correctly classify the clinical outcomes of interest. Face-to-face quality control was carried out through audits at 10–15% of centres in each country (1397 patients in total at baseline and follow-up visits). Fifteen patients (1%) were excluded from the database because of protocol deviations, and for 55 patients (3.9%) the quality of data was considered unsatisfactory due to the large number of missing parameters.

Physicians' adherence to guideline score

Physicians' adherence was assessed based on recommendations of the ESC HF guidelines in use at the time the study registry was established.[18] A score was developed for the five classes of medication recommended to reduce mortality and/or HF hospitalization: ACEIs, ARBs (if ACEIs not tolerated), BBs, MRAs [if New York Heart Association (NYHA) class II–IV] and ivabradine (sinus rhythm, NYHA class II–IV, and heart rate ≥ 70 or 75 b.p.m. (depending on local licensing regulations/marketing authorisation).[19] As under-dosage of recommended medications was identified as an issue in our baseline QUALIFY analysis,[19] we took account of dosage in our current adherence score by integrating adherence to TDs of recommended medications for both our previous 6-month outcome analysis[20] and the current 18-month analysis.

The adherence score was defined as the ratio of the treatment actually prescribed to the treatment that should theoretically have been prescribed. The theoretical treatment score was calculated for every patient, taking into account treatment eligibility criteria, guideline-based contraindications to drugs or treatments and use at ≥ 50% of recommended dosages. The number of patients prescribed medication at ≥ 50% TD was assessed using doses defined by the ESC guidelines when available;[15] for ivabradine, we used the target therapeutic regimen used in the Systolic Heart Failure Treatment with the I_f Inhibitor Ivabradine Trial (SHIFT).[21]

The score was calculated for each patient by summing the points attributed as follows: 0 points for non-prescription in the absence of contraindications, or prescription in the presence of contraindications; 0.5 points for the use of < 50% of TD (< 100% of TD for MRA as the majority of patients were treated with ≥ 50% of TDs of MRA) or 1 point for use in ≥50% of TDs (100% TD for MRA). Non-administration of recommended drugs due to recorded specific contraindications or intolerance was scored as adherence to guidelines. Physicians' adherence to guideline-recommended treatment was computed by dividing the actual treatment score by the theoretical treatment score and was considered as a continuous covariate ranging from 0 to 1.0. In this survey, our term 'adherence' relates solely to physicians following guidelines, not to patient compliance or persistence.

QUALIFY was carried out in accordance with the Declaration of Helsinki and was approved by relevant ethics committees and/or regulatory bodies in all 36 participating countries. All patients gave written informed consent to participate, in accordance with national and local regulations. The QUALIFY survey is registered in the ISRCTN registry of clinical trials under the number ISRCTN87465420.

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Statistical analysis

Study participants with no follow-up data, with incomplete baseline data for model fitting or incomplete time-to-event data were excluded from the analyses. Baseline characteristics of the study population are expressed as absolute and relative frequencies for categorical variables, mean ± standard deviation for approximately normally distributed continuous variables, and median (interquartile range) for non-normally distributed continuous variables. Comparisons concerning these characteristics between included and excluded cases were conducted using independent Student's *t*-test, Mann–Whitney U test, chi-squared test, and the Fisher's exact test.

Cumulative incidences for death or unplanned hospitalization attributable to HF or other CV or non-CV causes and associations of physicians' adherence to guideline-recommended treatment with respect to time-to-event with one event and multiple states were assessed in the framework of competing risks.[22]

Univariable analyses were also conducted for age, asthma, chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), coronary artery disease, diabetes mellitus, resting heart rate, hypertension, LVEF, sex, systolic blood pressure, and time since HF diagnosis. Statistically significant aforementioned variables were considered as covariates for multivariable Fine–Gray models concerning associations of physicians' adherence to guideline-recommended treatment with respect to time to event. Non-linearity in continuous covariates was determined using P-splines.[23] For fitted (multivariable) Fine–Gray models, the proportional subdistribution hazards assumption was assessed using (scaled) Schoenfeld residuals.[24] Overall survival was analysed in a similar fashion using proportional hazards models. Significance level was set at 5% and reported two-sided *P*-values were not adjusted for multiple comparisons due to the explorative nature of the investigation.

Reported exponentiated coefficients from the Fine–Gray models — the subdistribution hazard ratios (SHR) — can be interpreted as the relative change in the immediate rate of occurrence of the event of interest in subjects who are event-free or who have experienced a competing event for a 0.1 unit change in physicians' adherence score (adjusted for relevant covariates). All analyses were conducted using the cmprsk, stats and survival packages in R version 3.2.4.[25,26]

Results

A total of 7317 patients enrolled in the survey between September 2013 and December 2014 met eligibility criteria. The 18-month follow-up data were available in 6118 patients. *Figure 1* shows the reasons for excluding patients (3% of patients did not meet the inclusion criteria, 8% of patients did not have baseline data for adherence assessment, and 5% of patients did not have follow-up data).

The baseline characteristics are described in *Table 1* for the total population, i.e. both patients included in and excluded from the analyses (*Table 1*). For the included patients, the mean age was 62.8 years with a predominance of male patients (74.4%). Overall, 82.7% of patients were in NYHA class II or III and mean LVEF on echocardiography was 33.1 (10)%. Co-morbidities were frequently reported, including hypertension (64.5%), diabetes mellitus (34.5%), atrial fibrillation/flutter (28.3%), CKD (17.4%), COPD (11.4%), and peripheral arterial disease (9.5%). The rate of prescription was 66.5% for ACEIs, 21.3% for ARBs, 86.9% for BBs, 70.3% for MRAs, and 29.6% for ivabradine. However, recommended medications were often under-dosed since 27.3% of patients treated with ACEIs, 49.9% of those on ARBs and 48.5% of those on BBs received at least half of the dose recommended by the international guidelines. Under-dosage was also observed for ivabradine.

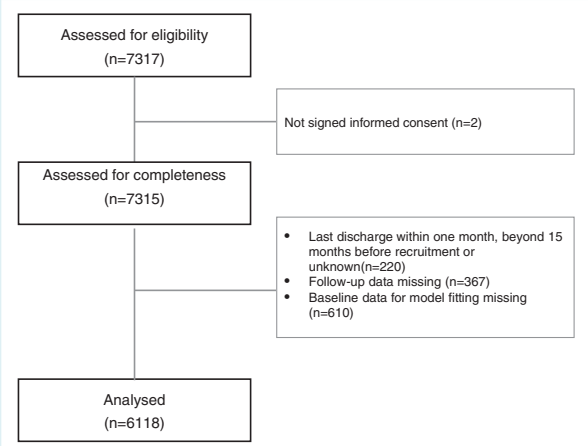

Figure 1 Patient population.

Excluded patients were on average older, were more often women, and were slightly more likely to have a history of CKD or COPD. They also had a lower rate of prescription of ACEIs, BBs and MRAs.

The observed distribution of physicians' adherence score ranging from 0 to 1 is shown in *Figure 2* and illustrates that in 50% of cases (score > 0.75) physicians adhered to guideline-recommended treatments closely.

The cumulative incidence of CV and non-CV clinical outcomes over the course of the 18-month follow-up was analysed (*Figure 3*). The cumulative incidence of death attributable to HF during the 18-month follow-up was also reported (*Figure 4*).

The association between clinical outcomes (unplanned hospitalizations or deaths) and physicians' adherence to HF medication is reported in *Table 2*. The majority of the reported deaths were attributable to CV causes. The majority of unplanned hospitalizations (1175 out of 1541, i.e. 76%) were due to CV causes. Among unplanned hospitalizations due to CV causes, the majority (861 out of 1175, i.e 73%) were related to unplanned hospitalizations for worsening HF. By univariable analysis, physicians' adherence to HF medication was found to be significantly associated with CV and HF deaths in our population. However, by multivariable analysis, only HF death and a composite of hospitalization attributable to HF or death attributable to CV death were associated with adherence. No significant association was found with any of the other analysed outcomes (*Figure 5*).

Discussion

Our data show that for a large population of patients with HFrEF who have previously been hospitalized for HF in 36 countries: (i)

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Table 1 Baseline characteristics of the study population

	Patients with data	Total sample ($n = 7315$)	Included ($n = 6118$)	Excluded ($n = 1197$)	*P*-value
Age (years)	7315	63.2 ± 12.6	62.8 ± 12.5	65.1 ± 12.6	<0.001
Male sex	7315	5400 (73.8)	4549 (74.4)	851 (71.1)	0.021
Ethnic origin	7312				<0.001
Caucasian		4205 (57.5)	3517 (57.5)	688 (57.5)	
Asian (including Middle East)		2207 (30.2)	1867 (30.5)	340 (28.4)	
HF duration (years)	7267	2.0 (4.0)	2.0 (4.0)	2.0 (5.0)	0.627
Coronary artery disease	7292	4140 (56.8)	3493 (57.1)	647 (55.1)	0.221
Atrial fibrillation/flutter	7293	2091 (28.7)	1730 (28.3)	361 (30.7)	0.105
Myocardial infarction	7235	3348 (46.3)	2847 (46.6)	501 (44.7)	0.274
Peripheral arterial disease	7230	678 (9.4)	582 (9.5)	96 (8.6)	0.352
Diabetes mellitus	7241	2488 (34.4)	2108 (34.5)	380 (33.8)	0.714
Hypertension	7219	4662 (64.6)	3947 (64.5)	715 (64.9)	0.812
Chronic kidney disease	7242	1288 (17.8)	1063 (17.4)	225 (20.0)	0.037
COPD	7243	849 (11.7)	696 (11.4)	153 (13.6)	0.037
Body mass index (kg/m^2)	7153	27.9 ± 5.4	27.9 ± 5.3	27.9 ± 5.9	0.992
Systolic BP (mmHg)	7295	126.3 ± 20.2	126.5 ± 20.1	125.5 ± 20.8	0.166
Diastolic BP (mmHg)	7294	76.1 ± 12.4	76.3 ± 12.3	75.1 ± 12.7	0.003
Resting heart rate (b.p.m.)	7288	76.3 ± 14.3	76.4 ± 14.3	76.2 ± 14.6	0.630
NYHA class	7280				0.003
I		902 (12.4)	730 (11.9)	172 (4.8)	
II		3365 (46.2)	2823 (46.2)	542 (6.5)	
III		2610 (35.9)	2235 (36.5)	375 (32.2)	
IV		403 (5.5)	327 (5.3)	76 (6.5)	
≥ 6 months since HF hospitalization	7209	3339 (46.3)	2787 (45.6)	552 (50.6)	0.002
LVEF (%)	6905	33.0 (10.8)	33.1 (10.0)	32.0 (11.0)	0.001
Fasting blood glucose (mmol/L)	5645	5.8 (2.2)	5.8 (2.2)	5.8 (2.3)	0.120
Serum creatinine (μmol/L)	6423	97.2 (39.0)	97.2 (37.0)	97.2 (45.4)	0.024
Haemoglobin (g/L)	6084	134.8 ± 20.4	135.1 ± 20.1	133.7 ± 21.9	0.069
eGFR (mL/min/1.73 m^2)	6420	63.8 (30.2)	64.1 (29.9)	60.9 (32.3)	0.001
Potassium (mmol/L)	5721	4.4 ± 0.5	4.4 ± 0.5	4.3 ± 0.6	0.035
Sodium (mmol/L)	5498	139.0 ± 4.3	139.2 ± 4.2	138.4 ± 4.4	0.001
ACEI	7293	4754 (65.2)	4067 (66.5)	687 (58.5)	<0.001
≥ 50% TD	4744	3436 (72.4)	2958 (72.7)	478 (70.6)	0.271
ARB	7290	1605 (22.0)	1305 (21.3)	300 (25.6)	0.002
≥ 50% TD	1288	637 (49.5)	532 (50.1)	105 (46.3)	0.322
BB	7290	6303 (86.5)	5318 (86.9)	985 (84.0)	0.010
≥ 50% TD	6235	3204 (51.4)	2740 (51.5)	464 (50.6)	0.631
MRA	7290	5044 (69.2)	4303 (70.3)	741 (63.2)	<0.001
100% TD	5041	3836 (76.1)	3290 (76.5)	546 (74.0)	0.159
Ivabradine	7180	2067 (28.8)	1808 (29.6)	259 (24.1)	<0.001
≥ 50% TD	2057	1755 (85.3)	1536 (85.3)	219 (85.5)	0.987
ICD	7227	702 (9.7)	572 (9.4)	130 (11.7)	0.019
CRT	7223	588 (8.1)	501 (8.2)	87 (7.8)	0.704
Non-CRT pacemaker	7219	432 (6.0)	354 (5.8)	78 (7.0)	0.130

Values are mean ± standard deviation, median (interquartile range), or *n* (%).
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; BP, blood pressure; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; TD, target dose.

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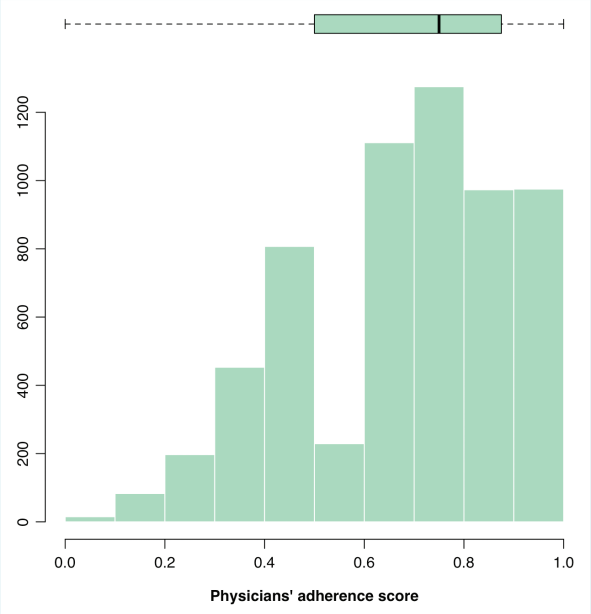

Figure 2 Histogram and boxplot representing the adherence score distribution of the studied population.

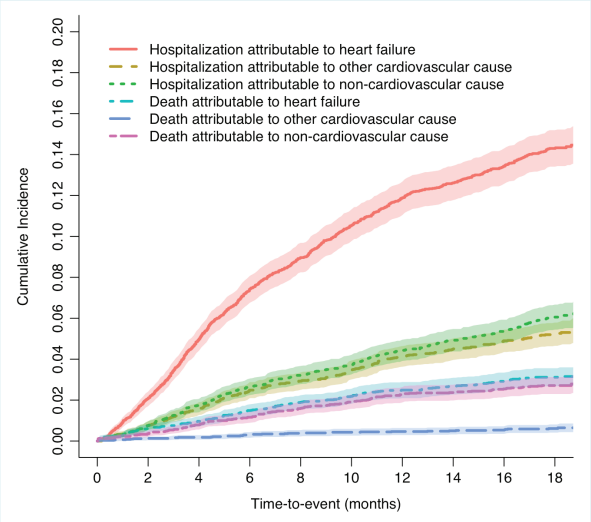

Figure 3 Cumulative outcome incidence during follow-up.

the majority of deaths and unplanned hospitalizations were CV and that among these, HF death and HF hospitalizations were highly prevalent, (ii) good physicians' adherence to guideline recommendations for five core groups of HF medications, with ≥ 50% of recommended dosages at baseline, was associated with better outcomes (reduction in CV and HF death) at 18-month follow-up according to univariable analysis, but after adjustment for baseline patient differences between the adherence categories this association persisted for HF death and a composite of hospitalization attributable to HF or death attributable to CV death, and (iii)

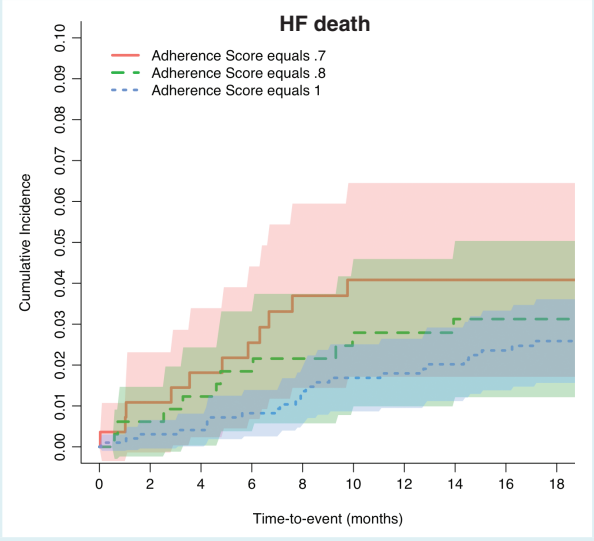

Figure 4 Cumulative incidences for cases with adherence scores 0.7 ($n = 276$), 0.8 ($n = 325$) and 1 ($n = 975$) as an illustrative example of the association between physicians' adherence to guideline-recommended treatment expressed as a score (0–1) and death attributable to heart failure (HF).

there was no significant association between physicians' adherence and unplanned CV or HF hospitalizations at 18-month follow-up.

The data from the recent prospective European BIOSTAT-CHF study in 2516 HF patients showed that those with HFrEF who were treated with less than 50% of recommended doses of ACEIs/ARBs and BBs seemed to have a greater risk of death and/or HF hospitalization than patients reaching at least 100% of recommended doses.[27]

Our data integrating five different classes of HF medications are in line with the BIOSTAT-CHF results since our scoring system integrated not only use of recommended classes in eligible patients, but also use of at least 50% of recommended dosages. Our findings provide further evidence supporting the clinical effectiveness of guideline-recommended HF therapies for patients encountered in real-world clinical practice and suggest that application of recommended drugs at a proper dosage is associated with improved HF mortality. The novelties of this analysis are related to: (i) the global nature of this registry, which enrolled a contemporary population of outpatients with HFrEF in 36 countries; (ii) the inclusion of both drug class adherence and dosage as components of our adherence score; (iii) the assessment of both fatal and non-fatal outcomes of key interest in HF; (iv) the collection of data over a longer period of follow-up (18 months); and (v) the inclusion of death as a competing risk in the analyses of HF hospitalization, in contrast to our previous analysis of shorter-term follow-up.[20] Given that a substantial number of deaths attributable to non-HF-related causes occur in patients with HF, a competing risk analysis increases the robustness of the data.

General adherence to guideline-recommended HF medication has improved over the past decade from approximately a quarter of prescriptions in 2008 to nearly two thirds in 2016.[7,19]

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Table 2 Relationship between physicians' guideline adherence score at baseline* and outcomes at 18 months

	Univariable analysis		Multivariable analysis	
	HR/SHR [95% CI]	*P*-value	HR/SHR [95% CI]	*P*-value
All-cause death[a] ($n = 394$)				
Adherence score*	0.96 [0.92;1.00]	0.073	0.97 [0.92;1.01]	0.172
CV death, including HF[b] ($n = 228$)				
Adherence score*	0.93 [0.88;0.99]	0.022	0.95 [0.89;1.01]	0.074
HF death[c] ($n = 191$)				
Adherence score*	0.91[0.86;0.97]	0.006	0.93 [0.87;0.99]	0.034
All cause unplanned hospitalization[d] ($n = 1541$)				
Adherence score*	1.00 [0.98;1.03]	0.808	0.99 [0.97;1.02]	0.520
Unplanned CV hospitalization[e] ($n = 1175$)				
Adherence score*	0.99 [0.97;1.02]	0.625	0.98 [0.96;1.01]	0.200
Unplanned HF hospitalization[f] ($n = 861$)				
Adherence score*	1.00 [0.97;1.03]	0.851	0.99 [0.96;1.02]	0.400
Hospitalization attributable to HF or death attributable to CV death[g] ($n = 1089$)				
Adherence score*	0.98 [0.96;1.01]	0.189	0.97 [0.94;0.99]	0.043

CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; SHR, subdistribution hazard ratio.

*The actual score of physician's adherence to guideline-conform treatment was used as dependent variable. Reported SHRs refer to a 0.1 unit change in adherence score.

[a]Derived from Cox proportional hazards models, adjusted for age, chronic kidney disease, chronic obstructive pulmonary disease, coronary artery disease, resting heart rate, hypertension, left ventricular ejection fraction, systolic blood pressure, and time since HF diagnosis.

[b]Derived from multivariable Fine–Gray model, adjusted for age, chronic kidney disease, resting heart rate, hypertension, left ventricular ejection fraction, systolic blood pressure, and time since HF diagnosis.

[c]Derived from multivariable Fine–Gray model, adjusted for age, chronic kidney disease, chronic obstructive pulmonary disease, coronary artery disease, diabetes mellitus, hypertension, left ventricular ejection fraction, systolic blood pressure, and non-linear time since HF diagnosis.

[d]Derived from multivariable Fine–Gray model, adjusted for age, chronic kidney disease, chronic obstructive pulmonary disease, coronary artery disease, diabetes mellitus, resting heart rate, hypertension, left ventricular ejection fraction, systolic blood pressure, and non-linear time since HF diagnosis.

[e]Derived from multivariable Fine–Gray model, adjusted for age, chronic kidney disease, chronic obstructive pulmonary disease, coronary artery disease, diabetes mellitus, resting heart rate, hypertension, left ventricular ejection fraction, systolic blood pressure, and non-linear time since HF diagnosis.

[f]Derived from multivariable Fine–Gray model, adjusted for age, chronic kidney disease, chronic obstructive pulmonary disease, diabetes mellitus, left ventricular ejection fraction, systolic blood pressure, and non-linear time since HF diagnosis.

[g]Derived from fitted multivariable Fine–Gray model adjusted for age, chronic kidney disease, chronic obstructive pulmonary disease, diabetes mellitus, resting heart rate, non-linear left ventricular ejection fraction, non-linear systolic blood pressure, and non-linear time since HF diagnosis.

However, as we and others have previously shown, under-dosing remains widespread, with less than one-third of patients achieving guideline-recommended doses for most key medicines.[11,19,27]

Data on the impact of adherence to guideline-recommended HF medication on clinical outcomes in daily practice are limited, particularly in relation to adherence to TDs. Two observational studies have provided some evidence of a link between dose optimization and improved outcomes, including mortality,[27,28] but these were limited to a European perspective. Two recent studies, one in a Medicare population in the US[16] and the other in a Japanese population,[17] suggest that initiation and continuation of ACEIs and BBs are associated with reduced mortality up to 1 year but not with hospitalizations. Clinical trials have also provided some evidence of the benefits of dose optimization of individual agents on mortality and hospitalization (lisinopril,[12] losartan,[13] carvedilol[29]), while other studies of metoprolol CR/XL and bisoprolol have demonstrated similar risk reduction, irrespective of dosage.[30,31] The lower rates of HF mortality, which persist after adjustment for baseline differences in patients, may at least in part reflect the benefits of disease-modifying medications and support the strategy of optimization of the guideline-recommended drugs.

By contrast, we observed no significant benefit on hospitalization rates at 18 months irrespective of the cause of hospitalization. The possibility that adherence had less impact on hospitalization than on mortality may be explained by the fact that hospitalization for HF is likely to be affected by several medical and non-medical factors.

Patient factors, such as co-morbidities, age, frailty, emerging contraindications of medications and adverse events, may all affect guideline adherence by physicians,[27] especially over time. Age also plays an important role and there is evidence that physicians are more likely to focus on symptom relief rather than on disease-modifying drugs in the advanced elderly.[32] Other factors may come into play, such as post-discharge inertia, economic factors and inadequate medical/prescription coverage, as well as the high out-of-pocket cost of drugs and limited or no access to long-term clinical follow-up and healthcare facilities. In addition, variation in communication between community and hospital-based services over long-term care and the intervention of different prescribers (i.e. general practitioners and nurses), with no clear identification of who was responsible for drug optimization, may have contributed to suboptimal dosing of medication.

The competing risk used in this paper is considered a robust statistical analysis and, indeed, we found similar results (lack of effect on hospitalizations) as in the two other recent studies which used this approach. Our data expand this observation by

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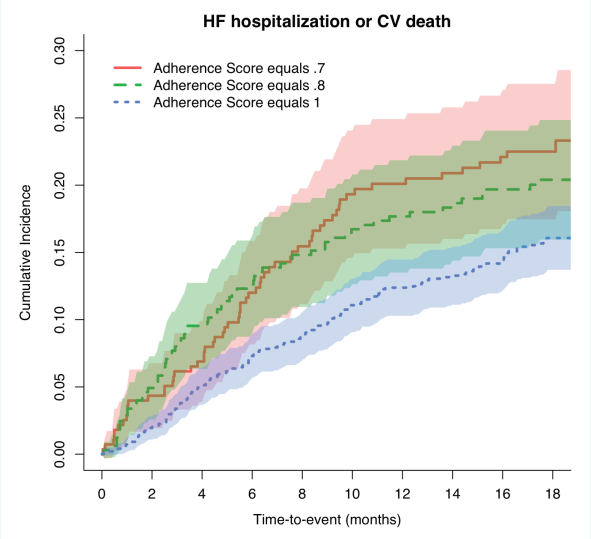

Figure 5 Cumulative incidences for cases with adherence scores 0.7 ($n = 276$), 0.8 ($n = 325$) and 1 ($n = 975$) as an illustrative example of the association between physicians' adherence to guideline-recommended treatment expressed as a score (0–1) and hospitalization attributable to heart failure (HF) or death attributable to a cardiovascular (CV) cause.

evaluating a more international population from 36 countries over five continents with different income levels and healthcare systems, and with patients followed up over a longer period of time. Results were generally similar across the different countries (grouped by geography or income level — data not shown), although these results need to be interpreted with caution due to the limited number of events in each group.

Limitations

There are several important limitations to our study. General factors include the relatively young age of our study population, which may not necessarily reflect the overall profile of HF in elderly patients. However, data from the Asian HF registry show that HF patients from Asia are significantly younger than those enrolled in Western countries (an average difference of 10 years),[33] so we believe that the young age of our population reflects the international nature of the QUALIFY registry.

Ninety per cent of QUALIFY patients were treated by cardiologists, and this does not reflect routine practice and may account for high and consistent levels of adherence, which may be harder to achieve in daily care. We thought that this influence may have decreased over time as the routine care of some patients was transferred to general practitioners and nurses working in the community. However, the overall proportion of patients who changed healthcare provider between baseline and the 18-month visit was small (5.9% patients).

QUALIFY centres were selected by national coordinators, on a voluntary basis, and selection bias cannot be excluded.

Our score was based on therapies recommended in the international guidelines, which were in use at the time QUALIFY was initiated.[18,34,35] Therefore, adherence and clinical outcome data related to neprilysin inhibitor therapy, which is recommended for use in HF in current international guidelines,[5,6] were not collected. We measured physicians' adherence and not patient compliance or persistence, which means that we were unable to assess the impact of these factors over the long follow-up period of this analysis.

The possibility of unmeasured bias, which exists in all observational studies, may have resulted in over- or underestimation of treatment effects. In addition, variability in investigator reporting cannot be excluded regarding the assessment of cause-specific mortality or hospitalization. Also, as is usually the case in observational studies, and in contrast to randomized clinical trials, there was no central adjudication for HF hospitalization. This may have played a role in the evaluation of this endpoint.

Conclusion

Overall, our data from a global registry suggest that physicians' adherence to guideline-recommended therapies for ambulatory HFrEF is associated with improved outcomes in HFrEF. We therefore urge improvement in physician and patient awareness of the disease, and guideline-recommended therapy, including more attention to uptitration of medication dosage, where possible.

Supplementary Information

Additional supporting information may be found in the online Supporting Information section at the end of the article.
Appendix S1. QUALIFY Committees and Investigators.

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Conflict of interest: M.K. reports personal fees from AstraZeneca, BMS, Menarini, Novartis, Amgen, Servier, MSD, Novo Nordisk and Sanofi, outside the submitted work. S.W. reports grants from Servier Affaires Medicales, during the conduct of the study. L.T. reports personal fees from Servier, during the

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References

1. Tavazzi L, Senni M, Metra M, Gorini M, Cacciatore G, Chinaglia A, Di Lenarda A, Mortara A, Oliva F, Maggioni AP. Multicenter prospective observational study on acute and chronic heart failure: one-year follow-up results of IN-HF (Italian Network on Heart Failure) outcome registry. *Circ Heart Fail* 2013;**6**:473–481.
2. Maggioni AP, Dahlström U, Filippatos G, Chioncel O, Crespo Leiro M, Drozdz J, Fruhwald F, Gullestad L, Logeart D, Fabbri G, Urso R, Metra M, Parissis J, Persson H, Ponikowski P, Rauchhaus M, Voors AA, Wendelboe Nielsen O, Zannad F, Tavazzi L; Heart Failure Association of the European Society of Cardiology (HFA). EURObservational Research Programme: regional differences and 1-year follow-up results of the Heart Failure Pilot Survey (ESC-HF Pilot). *Eur J Heart Fail* 2013;**15**:808–817.
3. Ambrosy AP, Fonarow GC, Butler J, Chioncel O, Greene SJ, Vaduganathan M, Nodari S, Lam CS, Sato N, Shah AN, Gheorghiade M. The global health and economic burden of hospitalizations for heart failure: lessons learned from hospitalized heart failure registries. *J Am Coll Cardiol* 2014;**63**:1123–1133.
4. Filippatos G, Khan SS, Ambrosy AP, Cleland JG, Collins SP, Lam CS, Angermann CE, Ertl G, Dahlström U, Hu D, Dickstein K, Perrone SV, Ghadanfar M, Bermann G, Noe A, Schweizer A, Maier T, Gheorghiade M. International REgistry to assess medical Practice with longitudinal obseRvation for Treatment of Heart Failure (REPORT-HF): rationale for and design of a global registry. *Eur J Heart Fail* 2015;**17**:527–533.
5. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2016;**18**:891–975.
6. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Colvin MM, Drazner MH, Filippatos G, Fonarow GC, Givertz MM, Hollenberg SM, Lindenfeld J, Masoudi FA, McBride PE, Peterson PN, Stevenson LW, Westlake C. 2016 ACC/AHA/HFSA focused update on new pharmacological therapy for heart failure: an update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *J Am Coll Cardiol* 2016;**68**:1476–1488.
7. Fonarow GC, Yancy CW, Albert NM, Curtis AB, Stough WG, Gheorghiade M, Heywood JT, McBride ML, Mehra MR, O'Connor CM, Reynolds D, Walsh MN. Heart failure care in the outpatient cardiology practice setting: findings from IMPROVE HF. *Circ Heart Fail* 2008;**1**:98–106.
8. British Society for Heart Failure. National Heart failure audit. https://www.nicor.org.uk/wp-content/uploads/2018/11/Heart-Failure-Summary-Report-2016-17.pdf (17 February 2017).
9. Savarese G, Carrero JJ, Pitt B, Anker SD, Rosano GM, Dahlström U, Lund LH. Factors associated with underuse of mineralocorticoid receptor antagonists in heart failure with reduced ejection fraction: an analysis of 11 215 patients from the Swedish Heart Failure Registry. *Eur J Heart Fail* 2018;**20**:1326–1334.
10. Chang LL, Xu H, DeVore AD, Matsouaka RA, Yancy CW, Fonarow GC, Allen LA, Hernandez AF. Timing of postdischarge follow-up and medication adherence among patients with heart failure. *J Am Heart Assoc* 2018;**7**:e007998.
11. Maggioni AP, Anker SD, Dahlström U, Filippatos G, Ponikowski P, Zannad F, Amir O, Chioncel O, Leiro MC, Drozdz J, Erglis A, Fazlibegovic E, Fonseca C, Fruhwald F, Gatzov P, Goncalvesova E, Hassanein M, Hradec J, Kavoliuniene A, Lainscak M, Logeart D, Merkely B, Metra M, Persson H, Seferovic P, Temizhan A, Tousoulis D, Tavazzi L. Are hospitalized or ambulatory patients with heart failure treated in accordance with European Society of Cardiology guidelines? Evidence from 12,440 patients of the ESC Heart Failure Long-Term Registry. *Eur J Heart Fail* 2013;**15**:1173–1184.
12. Packer M, Poole-Wilson PA, Armstrong PW, Cleland JG, Horowitz JD, Massie BM, Rydén L, Thygesen K, Uretsky BF. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. ATLAS Study Group. *Circulation* 1999;**100**:2312–2318.
13. Konstam MA, Neaton JD, Dickstein K, Drexler H, Komajda M, Martinez FA, Riegger GA, Malbecq W, Smith RD, Guptha S, Poole-Wilson PA; HEAAL Investigators. Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure (HEAAL study): a randomised, double-blind trial. *Lancet* 2009;**374**:1840–1848.
14. Yoo BS, Oh J, Hong BK, Shin DH, Bae JH, Yang DH, Shim WJ, Kim HS, Kim SH, Choi JO, Chun WJ, Go CW, Kang HJ, Baek SH, Cho JH, Hong SK, Shin JH, Oh SK, Pyun WB, Kwan J, Hong YJ, Jeong JO, Kang SM, Choi DJ; SUGAR Study. SUrvey of Guideline Adherence for Treatment of Systolic Heart Failure in Real World (SUGAR): a multi-center, retrospective, observational study. *PLoS One* 2014;**9**:e86596.
15. Komajda M, Lapuerta P, Hermans N, Gonzalez-Juanatey JR, van Veldhuisen DJ, Erdmann E, Tavazzi L, Poole-Wilson P, Le Pen C. Adherence to guidelines is a predictor of outcome in chronic heart failure: the MAHLER survey. *Eur Heart J* 2005;**26**:1653–1659.
16. Gilstrap LG, Fonarow GC, Desai AS, Liang L, Matsouaka R, DeVore AD, Smith EE, Heidenreich P, Hernandez AF, Yancy CW, Bhatt DL. Initiation, continuation, or withdrawal of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and outcomes in patients hospitalized with heart failure with reduced ejection fraction. *J Am Heart Assoc* 2017; **6**:e004675.
17. Yamaguchi T, Kitai T, Miyamoto T, Kagiyama N, Okumura T, Kida K, Oishi S, Akiyama E, Suzuki S, Yamamoto M, Yamaguchi J, Iwai T, Hijikata S, Masuda R, Miyazaki R, Hara N, Nagata Y, Nozato T, Matsue Y. Effect of optimizing guideline-directed medical therapy before discharge on mortality and heart failure readmission in patients hospitalized with heart failure with reduced ejection fraction. *Am J Cardiol* 2018;**121**:969–974.
18. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Køber L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Rønnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A, ESC Committee for Practice Guidelines. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the diagnosis and treatment of acute and chronic heart failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2012;**14**:803–869.
19. Komajda M, Anker SD, Cowie MR, Filippatos GS, Mengelle B, Ponikowski P, Tavazzi L; QUALIFY Investigators. Physicians' adherence to guideline-recommended medications in heart failure with reduced ejection fraction: data from the QUALIFY global survey. *Eur J Heart Fail* 2016; **18**:514–522.
20. Komajda M, Cowie MR, Tavazzi L, Ponikowski P, Anker SD, Filippatos GS; QUALIFY Investigators. Physicians' guideline adherence is associated with better prognosis in outpatients with heart failure with reduced ejection fraction: the QUALIFY international registry. *Eur J Heart Fail* 2017; **19**:1414–1423.
21. Swedberg K, Komajda M, Böhm M, Borer JS, Ford I, Dubost-Brama A, Lerebours G, Tavazzi L, SHIFT Investigators. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet* 2010;**376**:875–885.
22. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999;**94**:496–509.
23. Eilers PHC, Marx BD. Flexible smoothing with B-splines and penalties. *Stat Sci* 1996;**11**:89–121.
24. Grambsch P, Therneau T. Proportional hazards tests and diagnostics based on weighted residuals. *Biometrika* 1994;**81**:515–526.
25. Gray B. *cmprsk: Subdistribution Analysis of Competing Risks. R Package Version 2.2–27*. 2014. https://CRAN.R-project.org/package=cmprsk (4 March 2019).
26. R Core Team. *R: A Language and Environment for Statistical Computing. R Version 3.2.4*. R Foundation for Statistical Computing. http://www.r-project.org (4 March 2019).
27. Ouwerkerk W, Voors AA, Anker SD, Cleland JG, Dickstein K, Filippatos G, van der Harst P, Hillege HL, Lang CC, Ter Maaten JM, Ng LL, Ponikowski P, Samani

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NJ, van Veldhuisen DJ, Zannad F, Metra M, Zwinderman AH. Determinants and clinical outcome of uptitration of ACE-inhibitors and beta-blockers in patients with heart failure: a prospective European study. *Eur Heart J* 2017;**38**:1883–1890.
28. Poelzl G, Altenberger J, Pacher R, Ebner CH, Wieser M, Winter A, Fruhwald F, Dornaus C, Ehmsen U, Reiter S, Steinacher R, Huelsmann M, Eder V, Boehmer A, Pilgersdorfer L, Ablasser K, Kero D, Groebner H, Auer J, Jakl G, Hallas A, Ess M, Ulmer H; Austrian Working Group on Heart Failure. Dose matters! Optimisation of guideline adherence is associated with lower mortality in stable patients with chronic heart failure. *Int J Cardiol* 2014;**175**:83–89.
29. Bristow MR, Gilbert EM, Abraham WT, Adams KF, Fowler MB, Hershberger RE, Kubo SH, Narahara KA, Ingersoll H, Krueger S, Young S, Shusterman N. Carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure. MOCHA Investigators. *Circulation* 1996;**94**:2807–2816.
30. Wikstrand J, Hjalmarson A, Waagstein F, Fagerberg B, Goldstein S, Kjekshus J, Wedel H; MERIT-HF Study Group. Dose of metoprolol CR/XL and clinical outcomes in patients with heart failure: analysis of the experience in Metoprolol CR/XL Randomized Intervention Trial in Chronic Heart Failure (MERIT-HF). *J Am Coll Cardiol* 2002; **40**:491–498.
31. Simon T, Mary-Krause M, Funck-Brentano C, Lechat P, Jaillon P. Bisoprolol dose-response relationship in patients with congestive heart failure: a subgroup analysis in the Cardiac Insufficiency Bisoprolol Study (CIBIS II). *Eur Heart J* 2003;**24**:552–559.
32. Komajda M, Hanon O, Hochadel M, Lopez-Sendon JL, Follath F, Ponikowski P, Harjola VP, Drexler H, Dickstein K, Tavazzi L, Nieminen M. Contemporary management of octogenarians hospitalized for heart failure in Europe: Euro Heart Failure Survey II. *Eur Heart J* 2009;**30**:478–486.
33. Lam CS, Teng TH, Tay WT, Anand I, Zhang S, Shimizu W, Narasimhan C, Park SW, Yu CM, Ngarmukos T, Omar R, Reyes EB, Siswanto BB, Hung CL, Ling LH, Yap J, MacDonald M, Richards AM. Regional and ethnic differences among patients with heart failure in Asia: the Asian sudden cardiac death in heart failure registry. *Eur Heart J* 2016;**37**:3141–3153.
34. Jessup M, Abraham WT, Casey DE, Feldman AM, Francis GS, Ganiats TG, Konstam MA, Mancini DM, Rahko PS, Silver MA, Stevenson LW, Yancy CW. 2009 focused update: ACCF/AHA Guidelines for the diagnosis and management of heart failure in adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. *Circulation* 2009;**119**:1977–2016.
35. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL. 2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2013;**128**:1810–1852.

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